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Small cell carcinoma of the head and neck: An analysis of the National Cancer Database

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Abstract

Purpose/Objective(s)—To evaluate treatment trends and overall survival of patients with small cell carcinoma of the head and neck region.

Materials/Methods—Patients from 2004–2012 were identified from the National Cancer Database. Patient demographics and overall survival were analyzed. Multivariable analysis was used to identify predictors of survival.

Results—Among 347,252 head and neck patients a total of 1,042 (0.3%) patients with small cell carcinoma were identified. 17% of patients were diagnosed as stage I/II, 61% as stage III/IVA/IVB and 22% as stage IVC disease. The distribution by anatomic site was 9% oral cavity, 12% oropharynx, 35% larynx, 4% hypopharynx, 10% nasopharynx and 30% nasal cavity and paranasal sinuses. The median overall survival by anatomical site was 20.8 months for oral cavity, 23.7 months for oropharynx, 17.9 months for larynx/hypopharynx, 15.1 months for nasopharynx and 36.4 months for nasal cavity primary tumors. On multivariable analysis across stage, patients with nasal cavity and paranasal sinuses tumors had the best survival and patients with nasopharynx primaries had the worst survival. In stage I/II patients, type of treatment delivered resulted in no overall survival difference ($p=0.78$). In patients with locally advanced disease, there was no difference in survival between those treated with combined surgery, radiotherapy and chemotherapy compared to those treated only with radiotherapy and chemotherapy ($p=0.46$). The addition of radiotherapy to chemotherapy in the metastatic setting did not result in improved survival ($p=0.14$).

Conclusions—Small cell carcinoma of the head and neck is a rare malignancy with a poor prognosis. The addition of surgery to radiotherapy and chemotherapy did not improve survival in patients with locally advanced disease.

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Conflicts of Interest Notification: None

Keywords

small cell carcinoma; neuroendocrine carcinoma; head and neck cancer

Introduction

According to the World Health Organization, small cell carcinoma and poorly differentiated (grade III) neuroendocrine tumors are considered the same entity and are the most aggressive type of neuroendocrine carcinomas[1]. The histological category of neuroendocrine carcinomas includes carcinoid tumors, atypical carcinoid tumors and small cell carcinomas. Other synonyms for small cell carcinoma include small cell neuroendocrine carcinoma, oat cell carcinoma, anaplastic small cell carcinoma and small cell neuroendocrine carcinoma of intermediate type [2]. These tumors are defined microscopically by their small to intermediate sized cells, necrosis, large number of apoptotic cells, high mitotic rate, and lack of neurofibrillary stroma [1]. Electron microscopic examination usually show dense core secretory granules and abortive cell processes.[1] In addition, these tumors often stain positive for at least one neuroendocrine marker such as synaptophysin, CD 56, and chromogranin A[1].

Small cell carcinoma of the head and neck is a rare clinical entity. It's histological appearance is similar to small cell lung carcinoma.[1] Overall, these tumors are highly aggressive, associated with smoking and can occur throughout the head and neck region [3, 4]. The larynx, salivary glands and the sinonasal region are the most common sites for small cell carcinoma of the head and neck [2]. Given the rarity of this tumor, there is a paucity of clinical outcomes data available to guide treatment recommendations. A previous analysis has reported the outcomes of salivary gland small cell carcinomas [5, 6]; however, there is limited data on non-salivary gland head and neck small cell carcinomas. We performed an analysis of the National Cancer Database and report on the largest series of non-salivary gland, non-thyroid head and neck tumors classified as either small cell carcinoma or poorly differentiated neuroendocrine tumors.

Patients and Methods

Data Source

We conducted a population-based retrospective analysis utilizing the National Cancer Database (NCDB), which is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB integrates cancer registry records from more than 1,500 accredited hospitals and medical centers and collects data from approximately 70% of all newly diagnosed cancers in the United States [7]. Variables recorded in the database include patient demographics, stage, and interventions received (including surgery, radiotherapy and chemotherapy). The NCDB records overall survival but not local control or toxicity. The American College of Surgeons and the Commission on Cancer have not verified the data and are not responsible for either the analytic or statistical methodology used or the conclusions drawn from these data by investigators.

Study Cohort

Data for patients diagnosed with head and neck small cell carcinoma between 2004 and 2012 were obtained from the NCDB participant user files after appropriate approval. The participant user files included: lip, floor of the mouth, gum and other mouth, oropharynx, pharynx, tongue, tonsil, larynx, hypopharynx, nasopharynx, nose, nasal cavity and middle ear. A total of 347,252 patients made up these files and were queried for analysis. Tumors were queried based on their International Classification of Diseases for Oncology 3rd edition (ICD-O-3) code and included small cell carcinoma, NOS (8041), oat cell carcinoma (8042), small cell carcinoma fusiform cell (8043), combined small cell carcinoma (8045) and tumors coded as grade 3 neuroendocrine carcinoma NOS (8246). Patients with missing staging were excluded from this analysis. Figure 1 shows the breakdown of patients that were excluded and included.

Variables

Patient demographic and treatment information were dichotomized for purposes of univariate analysis and multivariable analyses in order to allow for reasonable comparisons. Age was analyzed as a continuous variable and Charlson-Deyo comorbidity score was analyzed as 0, 1, or 2. Race was dichotomized as white or non-white; insurance type as private or non-private; income as $\geq \$46,000$ or $< \$46,000$; location as urban ($\geq 250,000$ people) or nonurban ($< 250,000$ people); facility-type as academic or non-academic; clinical stage as I, II, III, IVA, IVB or IVC. Tumors were further classified as early stage (stage I/II), locally advanced (stage III/IVA/IVB) or metastatic (stage IVC). Tumors were grouped according to anatomical site, which included oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, nasal cavity/paranasal sinuses. Given the small number of hypopharynx primaries, larynx and hypopharynx were grouped together for survival analysis. Combining these two groups did not significantly change the survival outcomes. Treatments delivered included radiotherapy, chemotherapy and surgery. Details regarding chemotherapy drug names, dose, and treatment duration and details of concurrent or sequential chemotherapy in relation to radiation are not recorded. Patients who only had an excisional biopsy were excluded from the surgery group.

Statistical Analyses

For the overall survival analysis, the primary end point was defined as the time from diagnosis to death. Kaplan-Meier method and the log-rank test were used to determine median and 2-year overall survival. Univariate and multivariable analyses were performed using the Cox proportional hazard model. The proportional hazards assumption was checked graphically by using log-log survival plots and Schoenfeld residual plots. Variables were included in the multivariable analysis if significant or trending towards significance on univariate analysis. Statistical analyses were performed using SPSS (version 22, IBM SPSS, Armonk, NY). All p-values were two-sided, and a p 0.05 was considered statistically significant.

Results

Among the 347,252 patients with head and neck cancer within the NCDB from 2004–2012, there were a total of 1,042 (0.3%) patients identified as having small cell or poorly differentiated neuroendocrine tumors (Figure 1). Out of the 853 patients with staging information available, 542 (63.5%) were classified as small cell carcinomas and 311 (36.5%) classified as poorly differentiated neuroendocrine tumors. Patient characteristics of this cohort are given in Table 1. The median age of the patients included was 60 years and ranged from 18 to 90 years. The majority of patients were male (66%) and classified as white race (86%). Larynx (35%) and nasal cavity/paranasal sinuses (30%) were the most common anatomical sites. The majority of patients had stage III, IVA or IVB tumors (61%). Stage I and II tumors comprised 17% of the population while metastatic tumors represented 22%. Overall 55% of patients had lymph node positive disease. Table 2 shows the distribution of patients by stage and anatomical site.

Treatment by stage is listed in Table 3. When examining the entire cohort, radiotherapy was utilized in 69% of patients and chemotherapy in 78%. Overall, 61% of patients received combined chemotherapy and radiotherapy. The predominant treatments in patients with early stage disease was combined radiotherapy and chemotherapy (43%), surgery alone (16%) followed by radiotherapy alone (11%). 83% of patients with metastatic disease received chemotherapy.

Within the locally advanced group the majority of patients received combined chemotherapy and radiotherapy (54%). Of these, 40% started radiotherapy and chemotherapy within 14 days of each other and 41% started radiotherapy greater than 14 days from the start of chemotherapy. It is unknown, whether chemotherapy was given as induction prior to concurrent therapy or given as sequential therapy. There was no available treatment data on the other 9% of locally advanced patients. Surgery was used in 24% of locally advanced patients and trimodality therapy was used in 17% of these patients.

The median and 2-year overall survival of the entire cohort was 20.3 months and 45.2% respectively. The median overall survival and 2-year overall survival by anatomic site was 20.8 months and 44.5% for oral cavity, 23.7 months and 49.4% for oropharynx, 17.9 months and 40.6% for larynx/hypopharynx, 15.1 months and 30.3% for nasopharynx and 36.4 months and 55.4% for nasal cavity primary tumors. Overall survival stratified by stage and anatomical site is given in figure 2 and table 4. The median and 2-year overall survival for patients with lymph node positive disease was 20.8 months and 45.2% compared to 43.9 months and 62.3% for those without lymph node disease ($p<0.001$).

Univariate analysis and multivariable analysis for predictors of overall survival by stage are listed in the supplemental table and in Table 5, respectively. For early stage patients only primary site was predictive of overall survival. Patients with nasal cavity and paranasal sinuses had the best overall survival compared to the other sites. On univariate and multivariable analysis, there was no statistically significant difference in overall survival based on whether patients with stage I/II received definitive surgery, definitive chemoradiation or definitive radiation alone ($p=0.78$).

In patients with locally advanced disease, age, primary site and type of treatment were predictors of survival on multivariable analysis. Of note, there was no difference in overall survival between those treated with trimodality therapy consisting of surgery, radiotherapy and chemotherapy compared to those treated only with radiotherapy and chemotherapy ($p=0.46$) in the locally advanced group. This finding regarding surgery held true even when each subsite was individually analyzed: oral cavity ($p=0.12$), oropharynx ($p=0.72$), larynx/hypopharynx ($p=0.08$, trend of worse survival with surgery), nasal cavity and paranasal sinuses ($p=0.96$) and nasopharynx ($p=0.28$) (data not shown). For metastatic disease, having a nasopharynx tumor or not receiving chemotherapy correlated with a worse overall survival on multivariable analysis. The addition of radiotherapy to chemotherapy in the metastatic setting did not result in improved survival ($p=0.14$).

Discussion

This analysis represents the largest known series of small cell carcinoma of the head and neck. While the majority of small cell carcinomas are of lung origin, they can also originate from extrapulmonary sites.[8] Extrapulmonary small cell carcinomas make up 2.5–5% of all small cell carcinomas [2, 9]. Of the 2.5–5%, only 11–16% are head and neck small cell carcinomas [2]. We found that of the 347,252 cases of head and neck carcinoma in NCDB, only 1,042 (0.3%) patients had small cell carcinoma. Our findings demonstrate that small cell carcinomas are rare, aggressive and usually present in late stage with 61% of patients presenting as stage III, IVA or IVB tumors and 22% of patients presenting with metastatic disease. These findings are similar to other smaller series were Aguilar et al[10] reported a 17% incidence of distant spread at diagnosis and Hatoum,et al[11] reported 25% of their patients subsequently developed distant diffuse metastatic disease. Additionally, at the time of diagnosis, over half of the patients in this analysis had lymph node positive disease. Other smaller series report an incidence of cervical adenopathy in the range of 59–93%[11–13], with larynx cancers having the highest incidence[12].

The overall survival, in this analysis, for all patients with small cell carcinoma of the head and neck was 20.3 months. Not surprisingly, patients with early stage (I and II) disease experienced a better median survival of 49.0 months and 2-year overall survival of 69.1%, those with locally advanced stage (III, IVA, IVB) had an overall survival of 22.3 months and 2-year overall survival of 48.3%, and patients with metastatic disease had a poor median survival of 10.0 months and 2-year overall survival of 15.7%. In comparison, the median overall survival in locally advanced non-HPV associated head and neck squamous cell carcinoma is in the range of 30–40 months [14, 15] and the median survival of metastatic head and neck squamous cell carcinoma patients is typically around 6–12 months [16]. Small cell carcinoma of the head and neck appears to have a prognosis more similar to small cell carcinoma of the lung. Limited stage small cell carcinoma of the lung has a median survival of 18 to 24 months [17, 18] and extensive stage small cell carcinoma of the lung has an overall survival in the range of 10 to 12 months [17, 19].

The most common anatomical site for head and neck small cell carcinoma is the larynx [4, 20], which is consistent with our findings. Tobacco use and excessive alcohol use have been associated with small cell carcinoma of the larynx [2, 21]. The overall survival is poor in

these patients with laryngeal small cell carcinoma, with our results demonstrating a median survival of 17.0 months and a 2-year overall survival of 40.9%. Others, have reported two and five year survival rates of 16% and 5% respectively [20]. Small cell carcinoma of the paranasal and nasal cavity is also a common site of origin among head and neck primaries and in our data exhibited the longest overall survival with a median survival of 36.4 months and a 5-year overall survival of 45%. This finding held true when stratified by stage and on multivariable analysis. The majority of these paranasal and nasal cavity tumors presented as locally advanced cancers. The other largest series examining sinonasal small cell carcinomas, published by van der Laa et al, included a cohort of 115 patients obtained from a meta-analysis of 701 published studies[22]. This study found a 5-year disease-specific survival of 46% for these 115 patients with sinonasal small cell carcinoma. The authors found a non-significant trend for improved disease-specific survival with the use of surgery, however, they did not stratify patients by stage [22]. In our subgroup analysis no survival benefit was found with the addition of surgery to radiotherapy and chemotherapy ($p=0.96$) in locally advanced sinonasal small cell carcinomas. There were too few numbers to examine the role of surgery in the early stage patients. The improved survival compared to other disease sites, may be due to an observation noted by Baugh et al, that sinonasal small cell carcinomas tend to recur locally rather than as distant metastases, compared to laryngeal and pharyngeal sites [23]. The shortest overall survival was observed in patients with small cell carcinoma of the nasopharynx with a median survival of 15.1 months. There are no large series of small cell carcinoma of the nasopharynx to compare our results to. There only appears to be only a few published case reports [24, 25].

Management of localized small cell carcinoma of the head and neck includes a combination of surgery, radiation and chemotherapy [12, 26]; however, the recurrence rate is high and distant metastases occur often, especially when the disease involves the cervical lymph nodes. In non-metastatic disease, chemotherapy can be used in the neoadjuvant, concurrent or adjuvant setting to reduce tumor burden and decrease the risk of distant metastases. In this analysis, 61% of patients received combined chemotherapy and radiotherapy. Combined chemotherapy and radiotherapy was the most common treatment in both patients with early and locally advanced disease. While surgery has an important role in head and neck squamous cell carcinoma our findings show that the addition of surgery to radiotherapy and chemotherapy in patients with locally advanced disease did not result in improved survival when compared to patients treated with combined radiotherapy and chemotherapy. This finding held true even when individually examining each subsite. This finding is consistent with small cell carcinoma of the lung where surgical resection has a very limited role. In the early stage patients, overall survival did not differ by treatment approach indicating that surgery may have a role in these patients with limited disease burden.

In the metastatic setting, chemotherapy has been shown to prolong survival. [4, 23, 27]. In our analysis, 83% of patients with metastatic disease received chemotherapy. Chemotherapy regimens used in small cell carcinoma of the head and neck are similar to the regimens used in the management of small cell carcinoma of the lung, which typically include cisplatin and etoposide [28]. The type of chemotherapy given to the patients in this cohort was not known since this data is not available in the NCDB.

While the strength of the NCDB is its ability to provide large numbers for analysis of rare cancer types, there are limitations to such analyses. The most notable is that this is a retrospective database cohort review and specific treatment details are missing. The NCDB does not include details of chemotherapy type and cannot distinguish between sequential and concurrent chemoradiation. In addition, details such as PET-CT staging is missing and local control and toxicity are not available for analysis. Even with these limitations this analysis provides a considerable amount of valuable outcomes data that could not be obtained from small single institutional series.

In conclusion, small cell carcinoma of the head and neck represents a rare clinical entity, which is aggressive and has a poor prognosis. Of the patients with head and neck small cell carcinoma, those with nasopharyngeal and laryngeal origin exhibited the least favorable prognosis, while patients with paranasal and nasal cavity have the best outcomes. In patients with locally advanced disease surgery appears to have little impact on overall survival. This analysis is a valuable resource that will help clinicians inform patients about prognosis and guide treatment recommendations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research Highlights

- Small cell carcinoma of the head and neck is a rare and aggressive disease
- Larynx, nasal cavity and paranasal sinuses are the most common involved sites
- Nasopharyngeal and laryngeal sites have the worst prognosis
- Paranasal and nasal cavity have the best prognosis
- The addition of surgery showed limited benefit in locally advanced disease

Figure 1.
Inclusion and exclusion flow diagram

Figure 2. Overall Survival Kaplan Meier Plots by stage for (A) all sites, (B) oral cavity, (C) oropharynx, (D) larynx/hypopharynx, (E) nasopharynx and (F) nasal cavity/paranasal sinuses.

Table 1**Baseline Demographics and Patient Characteristics**

Total patients	853
Age at diagnosis	
Median (Range)	60 (18–90)
Sex	
Male	559 (65.5%)
Female	294 (34.5%)
Race	
White	733 (86.0%)
Black	89 (10.4%)
Other	31 (3.6%)
Charlson/Deyo comorbidity score	
0	679 (79.6%)
1	130 (15.2%)
2	44 (5.2%)
Insurance Type	
No insurance	45 (5.3%)
Medicaid/Medicare	448 (52.5%)
Private insurance	321 (37.6%)
Other government/Unknown	39 (4.6%)
Income	
<\$46,000	537 (63.0%)
\$46,000	274 (32.1%)
Unknown	42 (4.9%)
Location	
Non-urban	535 (62.7%)
Urban	282 (33.1%)
Unknown	36 (4.2%)
Facility	
Non-Academic	386 (45.3%)
Academic	424 (49.7%)
Unknown	43 (5.0%)
Year of Diagnosis	
2004–2006	208 (24.4%)
2007–2009	256 (30.0%)
2010–2013	389 (45.6%)
Tumor Location	
Oral Cavity	75 (8.8%)
Oropharynx	105 (12.3%)
Larynx	298 (34.9%)
Hypopharynx	34 (4.0%)

Nasopharynx	85 (10.0%)
Nasal Cavity and Paranasal Sinuses	256 (30.0%)
Overall Stage	
I	87 (10.2%)
II	60 (7.0%)
III	147 (17.2%)
IVA	279 (32.7%)
IVB	95 (11.1%)
IVC	185 (22.0%)

Table 2

Percent of patients by stage and anatomical site

	Oral Cavity	Oropharynx	Larynx	Hypopharynx	Nasopharynx	Nasal Cavity & Paranasal Sinuses
Stage I	13 (17.3%)	2 (1.9%)	36 (12.1%)	2 (5.9%)	7 (8.2%)	27 (10.5%)
Stage II	3 (4.0%)	5 (4.8%)	26 (8.7%)	1 (2.9%)	9 (10.6%)	16 (6.3%)
Stage III	12 (16.0%)	20 (19.0%)	45 (15.1%)	10 (29.4%)	23 (27.1%)	37 (14.5%)
Stage IVA	33 (44.0%)	41 (39.0%)	102 (34.2%)	11 (32.4%)	16 (18.8%)	76 (29.7%)
Stage IVB	1 (1.3%)	14 (13.3%)	12 (4.0%)	3 (8.8%)	12 (14.1%)	53 (20.7%)
Stage IVC	13 (17.3%)	23 (21.9%)	77 (25.8%)	7 (20.6%)	18 (21.2%)	47 (18.4%)

Table 3

Treatment by stage

	Stage I/II	Stage III/IVA/IVB	Stage IVC
No Treatment	13 (8.8%)	31 (6.0%)	16 (8.6%)
Surgery Alone	23 (15.6%)	18 (3.5%)	4 (2.2%)
Chemotherapy Alone	9 (6.1%)	45 (8.6%)	70 (37.8%)
Radiotherapy Alone	16 (10.9%)	27 (5.2%)	9 (4.9%)
Radiotherapy and Chemotherapy	64 (43.5%)	282 (54.1%)	72 (38.9%)
Surgery and Radiotherapy	2 (1.4%)	11 (2.1%)	1 (0.5%)
Surgery and Chemotherapy	5 (3.4%)	9 (1.7%)	6 (3.2%)
Surgery and Radiation and Chemotherapy	10 (6.8%)	89 (17.1%)	5 (2.7%)
Unknown Treatment	5 (3.4%)	9 (1.7%)	2 (1.1%)

Table 4

Overall Survival by site and stage

	Median OS (months)	2-year Overall Survival	Number of patients	p-value
All sites				<0.001
Stage I/II	49.0	69.1%	131 (17.3%)	
Stage III/IVA/IVB	22.3	48.3%	456 (60.1%)	
Stage IVC	10.0	15.7%	172 (22.7%)	
Oral Cavity				0.23
Stage I/II	36.8	66.7%	15 (22.7%)	
Stage III/IVA/IVB	18.8	42.4%	41 (62.1%)	
Stage IVC	8.3	20.0%	10 (15.2%)	
Oropharynx				<0.001
Stage I/II	25.0	57.1%	7 (7.5%)	
Stage III/IVA/IVB	43.1	59.6%	66 (70.1%)	
Stage IVC	7.9	12.0%	20 (21.5%)	
Larynx/Hypopharynx				<0.001
Stage I/II	29.1	65.3%	64 (21.5%)	
Stage III/IVA/IVB	19.1	42.3%	160 (53.9%)	
Stage IVC	10.8	14.2%	73 (24.6%)	
Nasopharynx				<0.001
Stage I/II	20.1	40.4%	16 (19.8%)	
Stage III/IVA/IVB	17.1	37.2%	49 (60.4%)	
Stage IVC	7.2	0%	16 (19.8%)	
Nasal Cavity/ Paranasal Sinuses				<0.001
Stage I/II	Not reached	91.0%	35 (15.8%)	
Stage III/IVA/IVB	53.9	55.4%	145 (65.3%)	
Stage IVC	8.9	25.2%	42 (18.9%)	

Table 5

Univariate and multivariable analyses by stage for factors predicting for overall survival

Stage I/II	Univariate Analysis				Multivariable Analysis			
	HR	(95% CI)	p-value		HR	(95% CI)	p-value	
Age at diagnosis (continuous)	1.02	1.001–1.046	0.04		1.02	0.99–1.04	0.21	
Charlson Comorbidity Index (0)	1.00				1.00			
1	1.25	0.59–2.65	0.57		0.95	0.44–2.04	0.89	
2	2.85	1.03–7.89	0.04		1.95	0.62–6.07	0.25	
Tumor Site (Nasal Cavity & Paranasal Sinuses)	1.00							
Oral Cavity	4.12	1.57–10.83	0.004		3.51	1.24–9.91	0.018	
Oropharynx	6.03	1.91–19.06	0.002		5.97	1.82–19.55	0.003	
Larynx/Hypopharynx	3.79	1.68–8.59	0.001		3.67	1.55–8.70	0.003	
Nasopharynx	4.86	1.80–13.11	0.002		3.57	1.25–10.17	0.017	
Treatment (Surgery +/- RT or chemotherapy)	1.00				1.00			
Radiotherapy and chemotherapy	0.92	0.34–2.48	0.87		0.59	0.21–1.67	0.32	
Radiotherapy alone	1.45	0.75–2.81	0.27		1.09	0.53–2.24	0.82	
Unknown or no treatment or other	2.05	0.95–4.44	0.068		1.62	0.77–3.73	0.25	
Stage III/IVA/IVB								
	Univariate Analysis				Multivariable Analysis			
	HR	(95% CI)	p-value		HR	(95% CI)	p-value	
Age at diagnosis (continuous)	1.03	1.02–1.04	<0.001		1.02	1.01–1.03	<0.001	
Charlson Comorbidity Index (0)	1.00				1.00			
1	1.56	1.15–2.12	0.005		1.35	0.97–1.87	0.072	
2	1.96	1.19–3.21	0.008		1.32	0.78–2.22	0.29	
Insurance (Private)	1.00				1.00			
Non-private/no insurance	1.47	1.16–1.87	0.002		1.09	0.83–1.43	0.56	
Tumor Site (Nasal Cavity & Paranasal Sinuses)	1.00				1.00			

Stage I/II	Univariate Analysis			Multivariable Analysis		
	HR	(95% CI)	p-value	HR	(95% CI)	p-value
Oral Cavity	1.42	0.91–2.22	0.12	1.62	1.00–2.39	0.046
Oropharynx	0.97	0.65–1.45	0.87	1.01	0.65–1.45	0.98
Larynx/Hypopharynx	1.65	1.23–2.22	0.001	1.60	1.07–1.99	0.006
Nasopharynx	1.73	1.16–2.59	0.007	1.85	1.15–2.63	0.005
Treatment (Chemotherapy alone)	1.00					
Chemoradiation	0.52	0.36–0.77	<0.001	0.56	0.38–0.84	0.005
Surgery and Radiation and Chemotherapy	0.45	0.23–0.73	<0.001	0.64	0.38–1.08	0.094
Other or no treatment	0.96	0.63–1.46	0.85	1.14	0.73–1.77	0.58
Stage IVC	Univariate Analysis			Multivariable Analysis		
	HR	(95% CI)	p-value	HR	(95% CI)	p-value
Age at diagnosis (continuous)	1.02	1.00–1.03	0.02	1.01	1.00–1.03	0.053
Insurance (Private)	1.00			1.00		
Non-private/no insurance	1.37	0.98–1.93	0.069	1.13	0.78–1.65	0.51
Tumor Site (Nasal Cavity & Paranasal Sinuses)	1.0			1.00		
Oral Cavity	0.72	0.41–1.29	0.28	0.86	0.40–1.89	0.71
Oropharynx	1.04	0.69–1.58	0.84	1.11	0.63–1.96	0.71
Larynx/Hypopharynx	0.93	0.70–1.23	0.63	0.99	0.65–1.51	0.97
Nasopharynx	1.58	1.02–2.45	0.043	2.03	1.09–3.77	0.026
Treatment (Chemotherapy alone)	1.00			1.00		
Radiotherapy and chemotherapy	0.77	0.53–1.12	0.17	0.78	0.53–1.15	0.21
Unknown or no or other treatment	1.56	1.02–2.41	0.042	1.62	1.04–2.52	0.033

* Only significant univariate analysis results shown. Full univariate analyses are listed in the supplemental table.