Second Primary Lung Malignancy Following Head and Neck Squamous Cell Carcinoma

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**Objectives/Hypothesis:** Analyze the characteristics of second primary lung malignancies (SPLMs) following an index head and neck squamous cell carcinoma (HNSCC).

**Study Design:** Retrospective cohort study.

**Methods:** The Surveillance, Epidemiology and End Results database was queried for all cases of HNSCC between 1973 and 2014 (N = 101,856). This population was compared to a standard population to assess relative risk for lung cancer, calculated as the standardized incidence ratio (SIR). Patients who developed SPLMs were extracted (N = 8,116) and compared to all other cases of lung cancer (N = 1,160,853) to assess histopathological differences. SPLM subpopulations divided by head and neck primary site were compared for lung cancer histology and time interval between cancer diagnoses.

**Results:** Overall, 8.0% of HNSCC patients developed SPLMs (SIR = 4.22, P < .001), diagnosed an average of 6.7 years later. Patients with HNSCC of the supraglottis and hypopharynx were at the highest risk relative to a standard population, with SIRs of 8.10 and 6.34, respectively. When comparing SPLMs to all other lung cancers, there was no difference in the distribution of lung lobe affected, but SPLMs were significantly more likely to be of squamous cell carcinoma histology (42.0% vs. 21.0%, P < .001). Among head and neck subsites, lung cancers following larynx tumors had a significantly higher proportion of squamous cell histology, and those following oropharyngeal or hypopharyngeal tumors had significantly higher proportions of squamous cell histology.

**Conclusions:** Patients who undergo curative treatment of HNSCC are at high risk for developing SPLMs. Subsite-specific differences may help elucidate the degree of risk attributable to smoking, genetic susceptibility, human papillomavirus infection, or metastasis masquerading as an SPLM.

**Key Words:** Otolaryngology, head and neck squamous cell carcinoma, second primary malignancy, lung cancer, smoking, retrospective, database.

**Level of Evidence:** 4

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INTRODUCTION

In patients who undergo curative treatment of head and neck squamous cell carcinoma (HNSCC), the leading cause of death is a second primary malignancy (SPM). HNSCC patients face significantly increased risk for SPLMs relative to the general population, with studies estimating a cumulative incidence over 15% at 5 years and 35% at 20 years following initial diagnosis. Of these second primaries, the greatest risk exists for lung cancer, which is responsible for nearly half of SPM-related mortality. Patients with second primary lung malignancies (SPLMs) have a significantly worse prognosis than those with an index lung cancer, with previous studies finding a mean survival time as short as 8 months and a 5-year survival rate of only 19%. HNSCC patients may face a significantly increased risk for lung cancer for a number of reasons, the most obvious being the shared risk factor of smoking. The concept of field cancerization refers to widespread mucosal changes that occur secondary to exposure to carcinogens such as tobacco and alcohol, which may explain the increase in risk for SPLMs of the aerodigestive tract. Other possible sources of SPLM risk may include a genetically conferred susceptibility or radiation exposure sustained in the diagnosis and treatment of the index cancer. However, it is difficult to determine what degree of risk is associated with each of these factors. Furthermore, the study of SPLMs may be subject to confounding when dealing with lung cancers of squamous cell histology, as it may be difficult to differentiate a second primary from a metastatic lesion.

Prior studies have explored risk factors for SPLMs by identifying predictive characteristics within the HNSCC population, including head and neck primary site. However, the literature is lacking any in-depth analysis of the lung cancer, which may provide additional etiological clues. Therefore, we sought to better understand SPLMs by comparing characteristics of these lung
cancers to those diagnosed in the general population, and assessing differences in lung cancer histology and timing of incidence between various head and neck subsites. This was done using the Surveillance, Epidemiology and End Results (SEER) database, which uniquely identifies patients with multiple primary malignancies and allows for a robust, population-based analysis.

MATERIALS AND METHODS

The SEER database was queried for all cases of HNSCC using the Multiple Primary-Standardized Incidence Ratios function. A case listing session was used to identify all patients with a first diagnosis of HNSCC recorded between 1973 and 2014 in the SEER-9 registries. Cases were identified as primaries of the head and neck using International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) codes for primary site, as listed in Table I. Primary sites were grouped as oral cavity, oropharyngeal, hypopharyngeal, or laryngeal, with notable subsites identified within each group. Cases of squamous cell carcinoma were selected for inclusion using relevant ICD-O-3 histology codes (8050–8089). Within this population, patients who subsequently developed lung cancer 22 months after their HNSCC diagnosis were identified and grouped as the SPLM cohort. Cases were identified as second primary malignancies (versus metastases) according to SEER criteria.

The SPLM cohort was first compared to the remaining population of HNSCC patients to identify significant differences in patient demographics and tumor characteristics including age, sex, race, stage, and grade (Table II). Tumor stage was given according to the American Joint Committee on Cancer 6th or 7th Edition staging, depending on the year of diagnosis. Tumor laterality was assessed when available for paired head and neck subsites. Significance was determined using Pearson χ² analyses.

The risk for SPLM associated with each primary HNSCC site and subsite was assessed using SEER’s calculation of Standardized Incidence Ratio (SIR) (Table III). The SIR represents the number of lung cancer cases observed in each HNSCC subsite divided by the number expected to be seen in a corresponding general population of the same size, matched for demographics. For each site, the average time interval between the diagnoses of HNSCC and SPLM was calculated (Table III). Significance was assessed by comparing the mean time interval for each individual subsite to the mean of all other subsites using independent two-tailed t tests. Competing risk analysis was used to best estimate the cumulative incidence of SPLMs among HNSCC survivors, with death attributable to the index HNSCC treated as a competing risk.

To assess the characteristics of the SPLM, SEER was again queried for all cases of lung cancer recorded over the same time period within the same registries. SPLM cases were compared to these index lung cancers for distribution of primary site, histology, and laterality (Table IV). For each of these characteristics, the average time interval between HNSCC and SPLM diagnoses was again assessed in the same manner as above. Lastly, the distribution of SPLM histology was assessed for lung cancers following each individual HNSCC primary site (Table V). Significance was measured through comparison of each subsite-specific histologic rate to the mean of all other subsites using Pearson χ² analyses.

All statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY). P values of < .05 were considered statistically significant. As per institutional guidelines, this analysis was determined to be exempt from institutional review board approval due to the deidentified nature of the dataset.

RESULTS

A total of 101,856 patients with HNSCC were identified in the SEER dataset. Of this population, 8,116 (8.0%)...
patients developed a second primary lung malignancy. When compared to the remaining population of HNSCC patients, those with a SPLM were significantly more likely to be of white race and male sex, and aged between 50 and 80 years. With regard to the index tumor, patients who developed SPLMs were more likely to have had an HNSCC that is stage III and moderately differentiated (Table II).

In assessing risk by primary head and neck site, all were found to have significantly increased risk relative to a standard population. The oropharynx (excluding base of tongue and tonsils), hypopharynx, and supraglottis carried the highest risk, with SIRs of 6.14, 6.34, and 8.10, respectively (Table III). The average time interval between the diagnoses of HNSCC and SPLM was 6.7 years, with 18% of SPLM cases diagnosed within the first year. Significant differences were found to exist in the average interval to SPLM incidence by subsite, with SPLMs following base of tongue, overall oropharynx, and hypopharynx tumors diagnosed 1 to 2 years earlier than the mean at 4.7 to 5.5 years. SPLMs following laryngeal and specifically glottic cancers were diagnosed approximately 1 year later than the mean (Table III). In patients surviving their index HNSCC, the cumulative incidence of SPLMs by primary site and subsite is depicted in Figures 1 and 2.

SEER identified 1,160,853 cases of index lung cancers for comparison. With regard to primary site, SPLM cases demonstrated a similar predilection for the upper lobes and the right side. The distribution of lung cancer location only differed at the main bronchi, with a lower proportion of these tumors seen in SPLM cases (5.2% vs. 6.2%, \( P = .001 \)). There were significant differences in the distribution of all histologic types except for large cell carcinoma. Patients with SPLMs were significantly more likely to be diagnosed with a lung cancer of squamous cell histology (42.0% vs. 21.0%, \( P < .001 \)), and less likely to be diagnosed with small cell (11.0% vs. 13.2%, \( P < .001 \)) or adenocarcinoma (21.0% vs. 32.9%, \( P < .001 \)) (Table IV). Squamous cell SPLMs were diagnosed 0.9 years earlier than the mean \( (P < 0.001) \), whereas adenocarcinoma SPLMs were diagnosed 0.8 years later. There was no significant difference in the mean time to SPLM diagnosis.

The distribution of SPLM histology was assessed within each subsite of the head and neck and compared to the overall distribution of SPLM histologic types (Table V). The rates of squamous cell carcinoma were the most variable, and a significantly higher proportion of squamous cell carcinoma was seen following primaries of the oropharynx, specifically the base of tongue and hypopharynx. Within the larynx, the proportion of squamous cell carcinoma SPLMs varied by subsite, representing 45% of SPLMs following supraglottic tumors but only 36% following glottic tumors. SPLMs following laryngeal tumors, including both glottic and supraglottic, had significantly increased rates of small cell histology.

### DISCUSSION

HNSCC patients face significant risk for a second primary lung cancer, which frequently represents a fatal diagnosis.\(^5,6\) In this analysis, this risk is estimated to be greater than four times what would be expected in a standard population. Older studies have applied similar methods to SEER data through 2006 to 2007, reporting slightly lower standardized incidence ratios of between 3.3 and 3.8.\(^10,12\) It should be considered that the lifetime risk for SPLMs may be increasing as a function of changes in HNSCC incidence patterns or treatment outcomes over time.\(^15\) Therefore, it is important to elucidate...
In evaluating the patient and tumor-related characteristics most strongly associated with SPLM incidence, prior studies have similarly identified significant disparities in risk between major head and neck primary sites. These site-specific differences have been previously attributed to human papillomavirus (HPV) status, with HPV-positive HNSCC patients carrying lower risk for SPM development. In this analysis, the evaluation of specific subsites allows for a better understanding of this risk, which we find is not necessarily uniform within each of the major sites. Within the oropharynx, base of tongue and tonsilar cancers carry less risk for subsequent SPLM development than the remaining oropharyngeal subsites, which is consistent with the knowledge that these two sites have significantly higher rates of HPV positivity. However, there are certainly other factors at play, as seen by the dramatic difference in SPLM risk between glottic and supraglottic tumors. Although these neighboring subsites have the same environmental exposures, it is well understood that supraglottic primaries carry a higher risk for metastatic spread due to their rich lymphatic supply. This may suggest the presence of lung metastases misclassified as SPLMs.

To contextualize these results, it is important to examine the criteria by which SEER classifies a tumor as a second primary and rules out the possibility of metastasis. Although standardized criteria exist, studies have shown that it is difficult to accurately differentiate SPLMs from metastatic lesions using basic clinical and histologic evaluation. SEER provides extensive guidelines to help coders determine if two tumors should be documented as a single or multiple primaries; however, these guidelines are only to be applied to “tumors not described as metastasis” in the patient record. SEER does not specify the level of evidence that is needed to rule out the possibility of metastasis, and this is left up to the reporting institution to determine. In two tumors with different anatomical sites but the same histology, advanced testing, such as gene expression profiling, can be used to help determine if they are of the same origin. However, the degree of scrutiny employed in each case is not recorded in SEER. Assessment of the accuracy of this determination is of value as it carries major implications on treatment selection and prognosis.

Comparison of lung cancer characteristics between SPLMs and index cases provides insight into the possibility of misclassified metastasis. Interestingly, these results find no significant difference in the distribution of lung lobe affected, which may suggest that metastatic lesions are unlikely to account for a significant proportion of the SPLM cohort. Although metastases to the lung typically present as multiple peripherally located nodules, those that occur as single metastatic lesions are more likely to be distributed in the basal portion of

**TABLE V.** Distribution of Second Primary Lung Cancer Histology by Head and Neck Subsite.

<table>
<thead>
<tr>
<th>Subsite</th>
<th>Squamous Cell (%)</th>
<th>Adenocarcina (%)</th>
<th>Small Cell (%)</th>
<th>Large Cell (%)</th>
<th>Other or NOS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>39.9</td>
<td>22.3</td>
<td>10.1</td>
<td>4.7</td>
<td>23.0</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>39.8</td>
<td>23.5</td>
<td>8.6*</td>
<td>5.2</td>
<td>23.0</td>
</tr>
<tr>
<td>Tongue (nonbase)</td>
<td>42.7</td>
<td>19.1</td>
<td>10.5</td>
<td>4.0</td>
<td>23.7</td>
</tr>
<tr>
<td>Other</td>
<td>37.3*</td>
<td>23.8</td>
<td>11.7</td>
<td>4.7</td>
<td>22.5</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>45.4†</td>
<td>20.3</td>
<td>11.1</td>
<td>3.0†</td>
<td>20.1</td>
</tr>
<tr>
<td>Base of tongue</td>
<td>51.9†</td>
<td>17.7</td>
<td>7.7*</td>
<td>2.0*</td>
<td>20.6</td>
</tr>
<tr>
<td>Tonsils</td>
<td>43.3</td>
<td>20.3</td>
<td>11.6</td>
<td>3.4</td>
<td>21.3</td>
</tr>
<tr>
<td>Other</td>
<td>41.7</td>
<td>22.9</td>
<td>13.8*</td>
<td>3.4</td>
<td>18.2</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>47.7*</td>
<td>17.5*</td>
<td>7.4*</td>
<td>5.3</td>
<td>22.2</td>
</tr>
<tr>
<td>Larynx</td>
<td>40.2*</td>
<td>12.5</td>
<td>12.1*</td>
<td>4.8</td>
<td>21.3</td>
</tr>
<tr>
<td>Glottis</td>
<td>35.7†</td>
<td>24.6†</td>
<td>12.1*</td>
<td>5.3</td>
<td>22.3</td>
</tr>
<tr>
<td>Supraglottis</td>
<td>44.6*</td>
<td>18.8*</td>
<td>12.2*</td>
<td>4.0</td>
<td>20.4</td>
</tr>
<tr>
<td>Other</td>
<td>44.5*</td>
<td>17.5</td>
<td>11.8</td>
<td>5.5</td>
<td>20.7</td>
</tr>
<tr>
<td>Overall</td>
<td>42.0</td>
<td>21.0</td>
<td>11.0</td>
<td>4.4</td>
<td>21.6</td>
</tr>
</tbody>
</table>

*P < .05.
†P < .001.
NOS = not otherwise specified.

Fig. 1. Second primary lung malignancy cumulative incidence by head and neck squamous cell carcinoma (HNSCC) primary site.
Therefore, we would expect to see some difference in the distribution of SPLM lung lobe involvement if a significant portion of these tumors had developed from metastatic spread.

In contrast, significant differences exist in the proportion of histologic types between SPLMs and index lung cancers. Squamous cell carcinomas represent the vast majority of SPLM cases, and are observed twice as often as in lung cancers in the general population. In assessing the etiology of this difference, the influence of smoking should certainly be considered. Prior studies have measured the relative risk conferred by smoking for each type of lung cancer histology, finding the odds ratio associated with squamous cell carcinoma development to be double to triple those for large cell or adenocarcinoma.24,25 In this cohort of SPLM patients, the increase in the proportion of squamous cell carcinoma development to be double to triple those for large cell or adenocarcinoma. However, smoking has been shown to be most strongly associated with lung cancers of small cell histology, even more so than squamous cell carcinoma.24,25 In this cohort of SPLM patients, the increase in the proportion of squamous cell carcinoma lung cancers is not accompanied by an increase in the rate of small cell cancers. Therefore, it is unlikely that smoking alone is to blame for the squamous cell carcinoma–related risk in SPLMs. This is once again supported by the similarity in the distribution of primary lung site between SPLMs and other lung cancers, as prior analyses have found that heavy smokers are more likely to develop tumors of the upper lobe.26,27

With smoking and metastasis unable to account for this specific increase in risk for squamous cell carcinoma SPLMs, additional consideration should be given to the possibility of a genetically determined susceptibility. This may exist as a somatic or germline mutation or as polymorphisms that either increase the propensity for de novo mutations or increase vulnerability to carcinogens such as cigarette smoke.28 For example, functional polymorphisms have been identified in the gene encoding EPHX1, which is an enzyme responsible for the metabolism of several carcinogens found in cigarette smoke. These variants have been shown to have different degrees of enzyme activity, and have therefore been implicated in the development of smoking-related cancers.29 Although there is much to be learned about the genetic determinants of cancer risk, it is certainly conceivable that the propensity to develop squamous cell carcinoma of both the head and neck and the lung is genetically influenced.

Additional insights can be gained from the assessment of SPLM histology by primary HNSCC subsite. In lung cancers following SCC of the larynx, significantly higher rates of small cell carcinoma were observed relative to other head and neck subsites. With the knowledge that small cell histology is the most strongly associated with smoking, this finding supports our understanding of laryngeal cancer as the head and neck malignancy most closely linked to smoking.30

Within the SPLM population, lung cancers following tumors of the base of tongue, overall oropharynx, and hypopharynx were significantly more likely to be of squamous cell histology. The single highest rate was observed following base of tongue cancers, where over half of SPLMs were found to be squamous cell carcinoma. Once again, the role of HPV positivity should be considered. Interestingly, prior studies of lung cancer have identified HPV positivity in up to 15% of those diagnosed in the United States,31 with the highest rates in lung cancers of squamous cell histology.32,33 Several authors have concluded that the prevalence of HPV16/18 infection in lung squamous cell carcinoma may therefore suggest a pathogenic mechanism.34,35 However, there is significant variability in the rate of HPV-positive lung cancers reported between studies,31 and many have argued that a causal relationship cannot be established.36,37 Bishop et al. assessed HPV status in 220 cases of SPLM SCC following HNSCC, finding 5% of these lung cancers to be HPV-positive. All of these cases followed oropharyngeal index tumors, 95% of which were HPV-positive as well. The authors concluded that these HPV-positive lung cancers were therefore more likely to be metastatic lesions than second primaries, despite being detected up to 8 years after primary HSNCC treatment.38 Advanced assessment techniques such as gene expression profiling...
may be employed in future study to better understand the nature and origin of these lung cancers.20

These same three subsites with the highest proportions of squamous cell carcinoma SPLMs were also found to have a significantly shorter interval between the diagnoses of HNSCC and SPLM, with lung cancer diagnosed an average of 1 to 2 years earlier than the mean. Once again, it should be considered that these cases may be more likely to represent a metastatic lesion that has been misidentified as a second primary. In HNSCC patients who develop distant metastases, studies have reported an average interval of 16 months between initial diagnosis and identification of distant disease,39 which is far shorter than the 6-year average interval observed in this analysis. The possibility of misclassified metastasis is supported by the increased rate of SPLMs seen following supraglottic cancers relative to the glottis, with a higher proportion of SCC histology and a shorter interval between diagnoses. In either case, these results reinforce the importance of lifelong posttreatment surveillance in HNSCC survivors.

The limitations to this study include many inherent to population-based registries such as SEER. Most notably, SEER does not report the presence of risk factors such as tobacco and alcohol use. Knowledge of current versus former smoking status as well as total exposure measured in pack years would provide significant insight into smoking-associated risk. This is particularly true in light of the fact that posttreatment tobacco and alcohol use has been shown to significantly increase the risk for second primary neoplasms.40,41 Furthermore, SEER does not contain detailed information regarding the specifics or extent of treatment. There are no data pertaining to chemotherapy, and radiotherapy data were removed from the public research database in 2016. Therefore, we are unable to determine the effects of HNSCC treatment modality on lung cancer incidence. However, the strength of this analysis lies in the statistical power afforded by SEER, which allows for new insights despite these limitations.

CONCLUSION
Patients who undergo curative treatment of HNSCC are at high risk for developing a second primary lung malignancy, particularly in those with a tumor of the hypopharynx, supraglottis, or oropharynx other than base of tongue or tonsils. Lung cancers that follow laryngeal primaries are more likely to be of small cell histology than other head and neck subsites, which suggests an association with tobacco smoke exposure. Patients with index cancers of the base of tongue and overall oropharynx or hypopharynx are more likely to develop squamous cell carcinoma of the lung, diagnosed 1 to 2 years earlier than the average. This may be attributable to an increase in risk secondary to HPV infection, a genetically conferred susceptibility, or metastasis masquerading as a second primary neoplasm. Advanced assessment of SPLM tumors may help to elucidate the etiology of this risk, allowing for improved identification of susceptible patients, early detection, and optimal treatment selection.

BIBLIOGRAPHY


