Laryngeal Neuroendocrine Carcinoma: A Population-Based Analysis of Incidence and Survival

Ritam Ghosh1, Rahul Dutta1, Pariket M. Dubal1, Richard Chan Park, MD1, Soly Baredes, MD1,2, and Jean Anderson Eloy, MD1,2,3,4

No sponsorships or competing interests have been disclosed for this article.

Abstract
Objective. Laryngeal neuroendocrine carcinoma (LNEC) is a rare malignancy with various subtypes, each with different characteristics. Classification of these subtypes is used to delineate treatment and management, as most are clinically aggressive with poor prognosis. This study analyzes the characteristics and survival outcomes of LNEC using population-based data.

Study Design. Analysis of a population-based tumor registry.

Setting. Academic medical center.

Subjects and Methods. The Surveillance, Epidemiology, and End Results (SEER) database (1973-2011) was queried for LNEC cases. Data analyzed included patient demographics, incidence, treatment modality, and survival.

Results. In total, 257 LNEC cases were extracted from the SEER database. Sixty-three percent were male, and the mean age of diagnosis was 61.9 years. Most cases were located in the supraglottis (62.6%), were of the small cell carcinoma (52.9%) histologic subtype, and were grade IV (40.9%) and American Joint Committee on Cancer (AJCC) stage IV (59.4%). Surgery and radiotherapy were used as treatment modalities in 38.3% and 59.8% of patients, respectively. Overall 5-year disease-specific survival (DSS) for all LNEC was 30.2%, with lower grade, lower AJCC stage, and treatment with surgery having higher 5-year DSS.

Conclusions. LNEC often presents as an aggressive tumor at an advanced stage and has poor survival outcomes. Poor prognostic factors include high histologic grade, advanced stage disease, and not undergoing surgical resection. LNEC may be best treated depending on its histologic differentiation, with surgery being beneficial for early grade tumors while radiotherapy is inconclusive in its benefit for late-stage disease.

Keywords
neuroendocrine carcinoma, malignancy, SEER, demographic, incidence, disease-specific survival, laryngeal carcinoma, laryngeal malignancy, throat cancer, laryngeal neuroendocrine carcinoma

Received April 16, 2015; revised June 4, 2015; accepted June 12, 2015.

Within the head and neck region, the larynx is the most common location for neuroendocrine carcinoma (NEC).1 Although they account for less than 1% of all laryngeal tumors, laryngeal NEC (LNEC) represents the most common nonsquamous type and has been reported to occur mostly in the supraglottic region.1–5 Initial presenting symptoms and signs can be, but are not limited to, throat discomfort, dysphagia, hoarseness, and neck mass.6–8 LNEC can either be of neural or epithelial origin and can be further classified into different subtypes depending on histology.2

The first case of LNEC was described in 1955 by Blanchard and Saunders,9 which they referred to as a “chemodectoma.” Unbeknownst to them at the time, they were actually dealing with a paraganglioma, or a neuroendocrine tumor of neural origin.7 The term carcinoid was first used by Goldman et al10 in 1969, who discovered the atypical form that resembled carcinoid tumors often found in the appendix and small intestine. In 1972, Olofsson and Van Nostrand11 discovered the small cell neuroendocrine subtype, which was shortly followed by Duvall et al12 in 1983, who were the first to differentiate between atypical and typical, as well as the first to draw a distinction between well

1Department of Otolaryngology–Head and Neck Surgery, Rutgers New Jersey Medical School, Newark, New Jersey, USA
2Center for Skull Base and Pituitary Surgery, Neurological Institute of New Jersey, Rutgers New Jersey Medical School, Newark, New Jersey, USA
3Department of Neurological Surgery, Rutgers New Jersey Medical School, Newark, New Jersey, USA
4Department of Ophthalmology and Visual Science, Rutgers New Jersey Medical School, Newark, New Jersey, USA

Corresponding Author:
Jean Anderson Eloy, MD, Department of Otolaryngology, Rutgers New Jersey Medical School, 90 Bergen St, Suite 8100, Newark, NJ 07103, USA.
Email: jeanne.anderson.eloy@gmail.com
differentiated and moderately differentiated. Despite these discoveries, the terminology for these different tumors has been quite varied, ranging from “APUDomas” to “Kulschitzky cell carcinomas” to “reserve cell carcinomas.” In 2005, the World Health Organization (WHO) put forth new guidelines in its classification for head and neck tumors that stand as our most current methodology for differentiating these lesions.5

When they are of epithelial origin, the WHO classifies NEC into 3 subtypes: typical carcinoid, atypical carcinoid, and small cell carcinoma.2-4 They can be also classified into well differentiated (typical), moderately differentiated (atypical), and poorly differentiated (large cell and small cell).2-4

To diagnose NEC, one must use light microscopy to view certain characteristics, such as peripheral palisading of tumor nests, trabeculae, rosette formation, and glandular differentiation.13 Immunohistochemistry is done to differentiate between the subtypes. While these tumors may be rare in nature, recognizing the subtype in question is very important in determining the appropriate management due to the unique nature of the respective subtypes.

Atypical carcinoids are the most common LNECs.6 They have a male predominance and occur mostly in heavy smokers, although smoking may be a risk factor for all other subtypes as well.2 They are mostly located in the supraglottic area but can be very aggressive and often metastasize to lymph nodes, lungs, liver, pancreas, prostate, and breast.2,3 Thus, in terms of treatment, wide resection is indicated, with a partial supraglottic laryngectomy with neck dissection often required.2,3 Typical carcinoid LNECs rarely metastasize and are found mainly in the supraglottic area. Thus, conservative surgery is recommended, which usually necessitates a partial laryngectomy. Due to lack of lymph node metastasis, radiotherapy and/or chemotherapy are not recommended.2,3 Small cell type of LNECs are the most aggressive and lethal.6 These often present with distant metastases, and the primary source is often supraglottic.2,3,6

Due to the extensive spread, surgery is rarely indicated, with chemotherapy and radiotherapy being the treatment of choice.6

Given the rarity of LNEC, the literature is limited to mostly case reports and small retrospective case series. A recent meta-analysis on LNEC has been performed.14 That study reviewed 182 studies on LNEC and primarily analyzed heterogeneous data extracted from case reports and small case series. The Surveillance, Epidemiology, and End Results (SEER) registry is a valuable tool for evaluating heterogeneous data extracted from case reports and small cell cases. The SEER database to evaluate the incidence of LNEC, organized by patient demographics, treatment modalities, and long-term survival tends.

Materials and Methods

The SEER 18 database includes data from the years 1973 to 2011 from 18 cancer registries throughout the United States. Institutional review board approval was not necessary per the standing policy of Rutgers New Jersey Medical School (NJMS). Case selection was done using International Statistical Classification of Diseases for Oncology, Third Edition (ICD-O-3) topography and histology/behavior codes. Topography codes used were all laryngeal subsites, including glottis (C32.0), supraglottis (C32.1), subglottis (C32.2), laryngeal cartilage (C32.3), overlapping lesions of the larynx (C32.8), and larynx not otherwise specified (NOS) (C32.9). Histology/behavior codes used were various subtypes of NEC, including typical carcinoid (8240/3), atypical carcinoid (8249/3), large cell NEC (8013/3), small cell NEC (8041/3), and NEC NOS (8246/3).

SEER*Stat 8.2.1 (National Cancer Institute, Bethesda, Maryland) was used to extract patient data. Incidence data were reported per 100,000 people and age-adjusted to the 2000 US Standard Population (19 age groups—Census P25-1130) standard. Survival data used to calculate 5-year disease-specific survival (DSS) were exported to Microsoft Excel 2013 (Microsoft Corporation, Redmond, Washington). Both Kaplan-Meier and Cox proportional hazards regression analyses were carried out using JMP Statistical Discovery 12 (SAS Institute, Cary, North Carolina). Significance was calculated with a log-rank test for Kaplan-Meier curves, 2-proportion test when 2 variables were involved, and a χ² analysis when 3 or more variables were involved. A probability value (P value) of <.05 was considered significant for all data.

Results

Patient Demographics

In total, 257 cases of LNEC were isolated between 1973 and 2011 (Table 1). Significantly more males (63.0%) were diagnosed with LNEC (P < .0001). Most patients were white (82.1%), followed by black (12.5%) and other (5.1%) races, with the difference between whites and blacks being statistically significant (P < .0001). The mean age at diagnosis was 61.9 years. Most cases were localized in the supraglottis (62.6%), followed by glottis (12.5%), larynx NOS (11.3%), subglottis (6.6%), laryngeal cartilage (4.3%), and overlapping lesions (2.7%). Most cases identified were of the small cell carcinoma histology (52.9%), followed by NEC NOS (35.8%), large cell NEC (4.3%), malignant carcinoid (3.9%), and atypical carcinoid (3.1%). The incidence of LNEC was 0.0117 per 100,000 individuals from 1973-2011 and 0.0068 in 2011 alone. An incidence trend could not be established from the SEER database.

Patients were divided into regions, which included the Northeast (14.4%), the South (23.7%), the West (45.1%), and the Midwest (16.7%). Geographic regions were further broken down by sex and race, which showed a majority of cases being white and male (Table 2).

Grading and Staging

Histologic grade data were available for 68.5% of LNEC cases (Table 3). Most cases identified were grade IV (undifferentiated or anaplastic, 40.9%), followed by grade...
stage IV (59.4%), followed by stage I (20.8%), stage III (13.9%), and stage II (5.9%).

**Treatment Data**

Data regarding surgical intervention were available for 99.6% of LNEC cases (Table 3). Surgery was performed on 38.3% of patients. Radiotherapy treatment information was available for 98.8% of LNEC cases. In total, 59.8% of patients received radiotherapy (beam radiation, radioisotopes, radioactive implants, or combination).

**Survival Analysis**

Survival data were available for 185 cases (Table 4). Overall 5-year DSS for all LNECs identified in the SEER database was 30.2%. By subsite, malignancies of the laryngeal cartilage had the best prognosis (83.3%), followed by glottis (31.8%), supraglottis (31.4%), larynx NOS (21.5%), overlapping lesions of the larynx (20%), and finally subglottis (0%). Survival for low-grade (grade I or II) LNEC was significantly higher (60.2%) than high-grade (grade III or IV, 20.5%) ($P = .0005$) (Figure 1). Five-year DSS for patients receiving surgery (43.8%) was significantly higher than those not receiving surgery (25.9%) ($P = .0339$) (Figure 2). Five-year DSS was significantly higher for AJCC stage I or II LNEC (66.1%) than AJCC stage III or IV (7.2%) ($P = .0005$). Five-year DSS for patients receiving radiotherapy was 27.9% and 35.2% for patients not receiving radiotherapy; these results were not statistically significant ($P = .7973$).

**Cox Proportional Hazards Regression**

Table 5 lists hazards ratios (HRs) generated using subsite-specific DSS from the Cox proportional hazards regression model. Laryngeal cartilage was used as the reference value because it had the highest 5-year DSS. Relative to the laryngeal cartilage, LNEC in all other laryngeal subsites had poorer prognosis. The relative HRs were 5.70 for the glottis ($P = .0291$), 5.61 for the supraglottis ($P = .0191$), 12.94 for the subglottis ($P = .0016$), 8.91 for overlapping lesions of the larynx ($P = .0238$), and 7.16 for larynx NOS ($P = .011$).

**Discussion**

LNEC is a rare malignancy, classified as such by the National Institutes of Health (NIH) because it affects fewer than 200,000 people in the United States.$^4$ LNEC, while it

---

**Table 1. Patient Characteristics.**

<table>
<thead>
<tr>
<th>Total No.</th>
<th>Percentage</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases</td>
<td>257</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>&lt;.0001a</td>
</tr>
<tr>
<td>Male</td>
<td>162</td>
<td>63.0</td>
</tr>
<tr>
<td>Female</td>
<td>95</td>
<td>37.0</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td>&lt;.0001b</td>
</tr>
<tr>
<td>White</td>
<td>211</td>
<td>82.1</td>
</tr>
<tr>
<td>Black</td>
<td>32</td>
<td>12.5</td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>5.1</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean age at diagnosis, y</td>
<td>61.9</td>
<td></td>
</tr>
<tr>
<td>Subsite</td>
<td></td>
<td>&lt;.0001c</td>
</tr>
<tr>
<td>Glottis</td>
<td>32</td>
<td>12.5</td>
</tr>
<tr>
<td>Supraglottis</td>
<td>161</td>
<td>62.6</td>
</tr>
<tr>
<td>Subglottis</td>
<td>17</td>
<td>6.6</td>
</tr>
<tr>
<td>Laryngeal cartilage</td>
<td>11</td>
<td>4.3</td>
</tr>
<tr>
<td>Overlapping lesion of larynx</td>
<td>7</td>
<td>2.7</td>
</tr>
<tr>
<td>Larynx NOS</td>
<td>29</td>
<td>11.3</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td>&lt;.0001d</td>
</tr>
<tr>
<td>Malignant carcinoid</td>
<td>10</td>
<td>3.9</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>8</td>
<td>3.1</td>
</tr>
<tr>
<td>Large cell neuroendocrine carcinoma</td>
<td>11</td>
<td>4.3</td>
</tr>
<tr>
<td>Small cell carcinoma NOS</td>
<td>36</td>
<td>52.9</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma NOS</td>
<td>92</td>
<td>35.8</td>
</tr>
<tr>
<td>Geographical distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>1973-2011</td>
<td>0.0117</td>
</tr>
<tr>
<td></td>
<td>2011</td>
<td>0.0068</td>
</tr>
</tbody>
</table>

Abbreviation: NOS, not otherwise specified.

$^a$P value compares whites vs blacks.

$^b$P value compares each subsite via $\chi^2$ analysis with 5 degrees of freedom.

$^c$P value compares each histology via $\chi^2$ analysis with 4 degrees of freedom.

$^d$Rates are per 100,000 and age-adjusted to the 2000 US Standard Population (19 age groups—Census P25-1130) standard.

---

**Table 2. Geographical Analysis of Laryngeal Neuroendocrine Carcinoma by Race and Sex.**

<table>
<thead>
<tr>
<th>Region</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>White</th>
<th>Black</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northeast</td>
<td>37 (14.4)</td>
<td>28 (75.7)</td>
<td>9 (24.3)</td>
<td>33 (89.2)</td>
<td>4 (10.8)</td>
<td>0</td>
</tr>
<tr>
<td>Midwest</td>
<td>43 (16.7)</td>
<td>22 (51.2)</td>
<td>21 (48.8)</td>
<td>38 (88.4)</td>
<td>5 (11.6)</td>
<td>0</td>
</tr>
<tr>
<td>West</td>
<td>116 (45.2)</td>
<td>74 (63.8)</td>
<td>42 (36.2)</td>
<td>93 (80.2)</td>
<td>9 (7.7)</td>
<td>14 (12.1)</td>
</tr>
<tr>
<td>South</td>
<td>61 (23.7)</td>
<td>38 (62.3)</td>
<td>23 (37.7)</td>
<td>47 (77.0)</td>
<td>14 (23.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$Percentage out of total number of patients (257).
is the most common nonsquamous tumor of the larynx, accounts for less than 1% of all laryngeal malignancies.1,2,13 Our analysis supports this idea, as LNEC showed an overall average incidence of 0.0117 per 100,000 individuals between 1973 and 2011, as well as an incidence of 0.0068 in 2011 alone.

While LNEC is rare, it is very aggressive, can cause local destruction, and metastasizes distally depending on the subtype.3,14 This malignancy has been mostly described previously in case reports and retrospective case series. In the past, LNEC has been confused with adenocarcinoma, acinic cell carcinoma, and adenoid cystic carcinoma.2 The different subtypes within LNEC have often been mistaken for one another, as diagnostic criteria are disparate, and current recommendations are based on anecdotal evidence.14 Identifying population-based trends in the management of LNEC is important, as there is confusion within the literature regarding the role of treatment in terms of radiotherapy and chemotherapy vs surgery, which has severe implications on quality of life, disease progression, and overall survival.

Prior studies have reported mean ages of diagnoses ranging from the fourth to the seventh decade of life for LNEC.1-3,5,14 Consistent with that study, we found that the small cell type was the most common, accounting for 52.9% of cases, followed by NEC NOS (35.8%). Atypical carcinoid, which is historically the most common, was the least prevalent type in our study at 3.1%. The reason for this is not clear but may be due to...
difficulty in histological classification of these entities. There are reports of atypical cancers being mislabeled as typical cancers and vice versa.4,14 Because of this difficulty in tumor classification, atypical cancers may have been labeled as NEC NOS, which may have accounted for the latter being much more common than expected.

NEC cancers are most commonly found in the gastrointestinal tract or the bronchial tree. The larynx is the most common location within the head and the neck, with the literature identifying the aryepiglottic folds of the supraglottis as the most common location.2,8 The most common primary site in our study was the supraglottis followed by the glottis, which concurs with previous studies. In terms of survival, our study found that tumors with a primary site in the laryngeal cartilage had higher 5-year DSS (83.3%), while malignancies in the supraglottis were associated with a lower 5-year DSS (31.4%). Furthermore, LNEC of the supraglottis, the most common site in our study, was associated with an almost 6-fold greater hazard of death compared with LNEC of the laryngeal cartilage. It is not clear why the laryngeal cartilage had a much more favorable prognosis, but our results must be tempered with the fact that those cases represented only 6 of 183 total cases for which survival data are available and, therefore, this trend requires further investigation.

Survival statistics for LNEC have also varied by subtype and study. A study by Soga et al16 found a 5-year DSS for typical carcinoid at around 48%, while more recent studies cited a number closer to 100%.14 This can be possibly attributed to difficulties in classification and making an accurate histological diagnosis, as typical carcinoid represents a low-grade (I) cancer with a better reported prognosis than an atypical carcinoid or a small cell carcinoid, which have high grades (II/III) and a worse prognosis.14 In small cell carcinoid, which was the most prevalent subtype in our study, Gnepp17 reported that 73% of patients succumbed due to metastatic disease with a mean survival time of 9.8 months.

In our analysis, most tumors were either undifferentiated (grade IV) or poorly differentiated (grade III), accounting for 40.9% and 35.2% of the data, respectively. As expected, the best 5-year DSS was observed for cases with low histological grades (I/II) and early stage disease (I/II). For higher grade and later stage disease, our data indicate very poor outcomes, as grades III/IV had a 20.5% five-year DSS, and stages III/IV had a similarly low 7.2% five-year DSS. This goes along with the incidence data gained from our study, as small cell and NEC NOS tend to be of higher grades and later staging, as a reported 50% of patients with small cell NEC have positive lymph nodes at the time of diagnosis, and 90% of all patients develop distant metastases.6,17

Treatment of LNEC tumors has always been defined by the histological subtype. Lower grades, such as typical or atypical carcinoid, have been treated with surgery, most commonly a partial supraglottic laryngectomy.1-4,8,14 A neck dissection is often recommended in light of cervical node metastases, especially in the setting of atypical carcinoid, which has been reported to metastasize in up to 66% of cases.3,4,13,16 In higher grades such as small cell carcinoma, surgery is almost never indicated due to distant metastases, yet a combination of radiotherapy and chemotherapy has been shown to prolong survival.
up to 55 months.\textsuperscript{18} The role of radiotherapy in combination with surgery, on the other hand, is not clearly delineated for all subtypes, as there is some debate as to whether radiotherapy after surgery or adjuvant chemotherapy has any effect on survival. For example, in a study by Gillenwater et al,\textsuperscript{19} although they recommended surgical resection for atypical carcinoid, a few patients responded to radiotherapy and chemotherapy, which prompted the discussion about the benefits of a combined approach.\textsuperscript{4} However, van der Laan et al\textsuperscript{14} found that patients with atypical carcinoid who received radiotherapy had a lower DSS than those treated surgically. Furthermore, patients treated with radiotherapy after surgery did even worse, suggesting that radiotherapy has a limited role in the treatment of atypical carcinoid.\textsuperscript{13}

In the present analysis, most patients did not undergo surgery (61.7%) but were treated with radiotherapy (59.8%). Patients who did not undergo surgery had significantly poorer outcomes than those who had surgery (25.9% vs 43.8%). The 5-year DSS for patients treated with radiotherapy was 27.9% vs 35.2% for those not receiving radiotherapy; however, this result was not statistically significant. Explanations for this poor prognosis may be attributed to a high occurrence of small cell carcinoma in our sample, which has historically poor outcomes. Moreover, most of the patients included in this analysis had stage IV disease. Although one may surmise that multimodal therapy can be beneficial for these higher grade tumors, our study indicates that the role of radiotherapy with these tumors is inconclusive. While patients treated surgically had significantly higher survival, these patients may have had moderately differentiated disease (grade II) and early stage tumors (stage I), as these respectively comprised 21.0% and 20.8% of patients. These findings highlight that LNEC is an aggressive tumor in which careful histological analysis must be done to determine the most effective therapeutic modality.

To our knowledge, this study represents the first large-scale, population-based analysis of LNEC. A population-based data set such as SEER has limitations that must be taken into consideration. While SEER is able to compile extensive and standardized information compared with that analyzed in case series and case reports, and the important meta-analysis previously performed.

**Conclusion**

LNEC is a rare malignancy in which histologic differentiation delineates much of its character. It commonly affects white males and is primarily found in the supraglottis. Poor prognostic factors include high histologic grade, advanced stage, and nonsurgical treatment. Most of these tumors present as highly aggressive with late-stage disease. Surgery alone may show survival benefit for early and local disease. The value of radiotherapy is inconclusive for most tumors analyzed.

**Author Contributions**

Ritam Ghosh, acquisition of data, analysis, drafting, final approval; Rahul Dutta, acquisition of data, analysis, drafting, final approval; Pariket M. Dubal, acquisition of data, revision, final approval; Richard Chan Park, conception, revision, final approval; Soly Baredes, conception, revision, final approval; Jean Anderson Eloy, conception and design, analysis and interpretation of data, revision, final approval.

**Disclosures**

**Competing interests:** None.

**Sponsorships:** None.

**Funding source:** None.

**References**