Primary neuroendocrine neoplasm of the esophagus – Report of 14 cases from a single institute and review of the literature

Francisco TUSTUMI1, Flavio Roberto TAKEDA2, Rodrigo Hideki UEMA3, Guilherme Luiz Stelko PEREIRA2, Rubens Antonio Aissar SALLUM1 and Ivan CECCONELLO1

ABSTRACT – Background – Most prevalent esophageal neoplasm is squamous cell carcinoma and adenocarcinoma. Other tumors are uncommon and poorly studied. Primary neuroendocrine esophageal neoplasm is a rare carcinoma and most of its therapy management is based on lung neuroendocrine studies. Neuroendocrine tumors can be clustered in the following subtypes: high grade (small cell carcinoma or large cell carcinoma) and low grade (carcinoids). Objective – The present study aims to assess clinical and pathological neuroendocrine esophageal tumors in a single oncologic center. Methods – A retrospective analysis of patients and review of the literatures was performed. Results – Fourteen patients were identified as neuroendocrine tumors, 11 male and 3 female patients. Mean age was 67.3 years old. Ten patients were classified as small cell, 3 as large cell and 1 as carcinoid. Four patients presented squamous cell carcinoma simultaneously and 1 also presented adenocarcinoma. Main sites of metastasis were liver, peritoneum, lung and bones. Most patients died before 2 years of follow-up. Patient with longer survival died at 35 months after diagnosis. Conclusion – Neuroendocrine esophageal tumors are rare; affect mainly men in their sixties or seventies. High grade tumors can be mixed to other subtypes neoplasms, such as adenocarcinoma and squamous cell carcinoma. Most of these patients have poor overall survival rates.

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Main symptoms were dysphagia (14/14) and weight loss (mean 11.7 ± Std Dev 6.3 kg). Duration of symptoms prior to diagnosis was 6.2 ± Std Dev 3.3 months.

Associated squamous cell carcinoma could be seen in 4/14 cases and associated adenocarcinoma (adenoneuroendocrine) in 1/14. Immunohistochemical panel can be seen in Table 2.

Of these patients, 10/14 had previous history of high amount of alcohol intake and 12/14 were tobacco smokers.

Most cases were diagnosed at late stages (III and IV), accordingly AJCC 7th Edition\(^{12}\). Metastasis sites were lungs, liver, adrenal, peritoneal and bones.

Cause of death was pneumonia in five cases, urinary tract infection in one case, and sepsis of unknown origin in one case. The five remaining patients, cause of death was not clearly established.

Curative intent surgery was performed in 4/14 patients, of which one is still alive at 26 months of follow-up.

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### TABLE 1. Main characteristics of the 14 patients diagnosed with neuroendocrine tumor

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>KPS</th>
<th>ECOG</th>
<th>Stage</th>
<th>Histologic subtype</th>
<th>Associated neoplasm</th>
<th>Site</th>
<th>Survival (months)</th>
<th>Esophagectomy</th>
<th>Chemotherapy</th>
<th>Radiotherapy</th>
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<td>Lower</td>
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<td>Alive at 26 months</td>
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<td>2</td>
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<td>M</td>
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<td>1</td>
<td>IIIA</td>
<td>SCCE</td>
<td>No</td>
<td>Middle</td>
<td>Middle and lower</td>
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<tr>
<td>4</td>
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<td>Lower</td>
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<td>LCCE</td>
<td>EA</td>
<td>Lower</td>
<td>18</td>
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<td>XP</td>
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### TABLE 2. Immunohistochemical panel of patients with esophageal neuroendocrine neoplasm

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<tr>
<th>Patient</th>
<th>Grade of cellular differentiation</th>
<th>Syp</th>
<th>CgA</th>
<th>Ki-67(%)</th>
<th>Ber-EP4</th>
<th>Ck7</th>
<th>AE-1/AE-3</th>
<th>35BH11</th>
<th>P63</th>
<th>CD 56</th>
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(+): positive; (-): negative; Syp: Synaptophysin; CgA: Chromogranine A; Ck: Cytokeratin; NP: not performed.

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**FIGURE 1.** Endoscopic view of a high grade neuroendocrine neoplasm. It shows a circumferential infiltrative and ulcerating tumor.
Most cases had low survival rates (see Figure 2). Patient who lived longer died at 35 months of pneumonia. Patient “2” is still alive without disease up to this paper publication. Patients “6” lost to follow-up, with disease. The remaining patients died with disease.

Review of the literature

For review of the literature, a total number of articles by database search were 1007. After excluding duplicates and screening by title and abstract, 154 articles remained. A cumulative sample size of 2,957 patients was evaluated, in 20 different countries. Of this patients, 2,899 were SCEC (77% in East countries; 23% in West countries); 35 were LCEC (6% in East countries; 94% in West countries); and 23 were carcinoid (54% in East countries; 43% in West countries).

Among all esophageal malignancies, prevalence of SCEC was 1.05% in East countries and 0.72% in West countries. There are few studies data concerning carcinoid tumors and LCEC prevalence. Most of the studies approaching LCEC were performed in West countries.

Neoplasms were staged as limited disease (LD) or extend disease (ED). LD is defined as disease confined to the esophagus and adjacent organs with or without regional lymph node involvement while ED is defined for neoplasm with distant spread. Main features and differences concerning neuroendocrine subtypes are presented in Table 3.


discussion

Neuroendocrine esophageal neoplasms are exceedingly rare, and hence there are few large sample clinical studies approaching this issue. Consequently, most of the knowledge is based on neuroendocrine lung neoplasms.

Neuroendocrine lung tumors are classified as low grade (carcinoids) or as high grade (SCEC and LCEC). SCEC have nuclear appearance, with finely granular chromatin; lack of predominant nucleoli; nuclear fragility; fusiform cells; scant cytoplasm and indistinct cells borders; high mitotic rate; and large area of necrosis (Figure 3).
LCEC presents non-cell nuclear features (vesicular clumpy chromatin, predominant nucleoli), abundant cytoplasm, and large cell size\(^{120}\). (Figure 4).

![Figure 4](image-url)

**FIGURE 4.** Large cell esophageal carcinoma (LCEC). Solid nests of large and intermediate cells, with eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli, focal necrosis and high mitotic rate (a) (HE, 200x). Chromogranin positive (400x) (b).

Carcinoids typical morphology includes coarsely granular “sult and pepper” chromatin, overall uniformity, prominent vascularity, lack of prominent nucleoli, low mitosis rate. Usually no necrosis is seen\(^{120}\).

Esophageal high grade tumors tend to be aggressive. Usually, patients are diagnosed lately, with widespread disease, and with poor prognosis. Currently, clinical treatment strategies of high grade cancers neuroendocrine neoplasms are very limited and full of contradiction. High grade neoplasms are often regarded as a systemic disease and, just like in lung cancer, chemotherapy is the mainstay of therapy\(^{17}\). Additional therapy (surgery or radiotherapy) should be considered, but randomized controlled trials still unavailable\(^{80,116}\).

Our data suggests a much good prognosis for low grade neuroendocrine tumors, with high overall survival rate. For limited disease (LD) carcinoid, surgical intervention is the treatment of choice\(^{10}\).

Although low incidence of esophageal neuroendocrine tumors, our results give a better picture of the behavior of this rare condition. The present study shows this disease affects mainly men in sixties or seventies. Middle and lower esophageal thirds are most frequently affected. Nevertheless, future multicenter efforts are needed for randomized clinical trials evaluating therapeutic guidelines.

**ACKNOWLEDGMENT**

We would like to state our acknowledgment for Rafaela Brito Bezerra Pinheiro efforts on pathology analysis and microscopy pictures.

**Authors’ contributions**


**REFERENCES**


