A primary small cell carcinoma of the esophagus in a 61-year-old woman was treated by transthoracic esophagectomy. The clinical data were correlated with data obtained from a review of the 129 cases reported in the world literature, thereby providing a clinical profile and suggested management strategy for this rare type of esophageal malignancy. Presenting symptoms of esophageal small cell carcinoma include dysphagia (75.3%), weight loss (38.4%), and chest pain (23.3%). Treatment regimens have included surgical intervention in 58%, radiotherapy in 10%, chemotherapy in 6%, or some combination of these in 26%. Overall survival is only 20.7 weeks after diagnosis. The fact that three fourths of affected patients had metastatic disease at the time of diagnosis leads us to recommend surgical intervention plus systemic chemotherapy in these patients.


Material and Methods

The clinicopathological correlates of esophageal SCC have not been defined clearly in the surgical literature because most reports have been isolated clinical or pathological reviews of a single tumor or small series. The purpose of this review is to collect all evaluable data from the 129 patients with esophageal SCC reported in the literature and from our personal experience to develop an accurate clinical profile and management strategy.

Case Report

To illustrate one clinical approach to this tumor, the case of a patient with a primary SCC of the esophagus is presented. This 61-year-old woman was seen at The Johns Hopkins Hospital in April 1987 with a 2-year history of chest pain and mild dysphagia. The patient had undergone a barium esophagogram and cardiac evaluation approximately 18 months previously, which failed to disclose any abnormality. She denied any weight loss, gastrointestinal reflux symptoms, or fever. Physical examination revealed a well-appearing, mildly obese woman. Examination of the chest, abdomen, and lymph node-bearing areas was unremarkable. Admission blood studies were all normal. A computed tomographic scan of the chest and abdomen revealed a 6-cm mass in the midesophagus with a small left paraaortic lymphadenopathy. Esophagogastroduodenoscopy demonstrated an ulcerated polypoid mass in the midesophagus, 26 cm from the incisors, that filled approximately half of the esophageal lumen. Biopsy specimens revealed SCC of the esophagus.

In May 1987, the patient underwent a transthoracic esophagectomy with cervical esophagogastrostomy, cholecystectomy, and feeding jejunostomy. The postoperative course was complicated by an anastomotic leak, which was treated by open drainage, and a left chylothorax, which resolved with tube thoracostomy drainage and hyperalimentation. The patient was discharged home on the 35th postoperative day. She could tolerate a regular
diet and had refused adjuvant chemotherapy. One month after discharge, the patient moved to another state and was lost to follow-up.

Pathological examination revealed a 4.4 \times 3\text{-}cm raised, ulcerated midesophageal lesion extending to the deep margins of the specimen (Figs 1, 2). Microscopically the tumor showed in situ and infiltrating carcinoma with predominantly a small cell undifferentiated appearance and focal areas of squamous differentiation (Fig 3). Metastatic tumor was present in two periesophageal lymph nodes and a left gastric lymph node. Mucosal margins were negative for tumor.

**Review of Literature With Clinicopathological Correlations**

Including the index case, a total of 130 cases of SCC of the esophagus were reviewed [5, 7-43]. Available clinicopathological information was gathered from each reference to create summary statistics. Of the 130 patients, 61.4% were male and 38.6% were female. The mean age was 64 years (range, 29 to 88 years). The principal symptoms were dysphagia (75.3%), weight loss (38.4%), and chest pain (23.3%), and the mean duration of symptoms was 4.4 months. It is apparent that the presenting signs and symptoms are similar to those of patients with other, more common histological types of esophageal cancer. Ectopic endocrinopathic findings were noted in 2 patients [14, 27]. A history of alcohol or tobacco use was mentioned for very few patients and was not evaluable etiologically.

Tumor characteristics are summarized in Table 1. Squamous cell carcinoma of the esophagus is typically diagnosed at an advanced, metastatic stage with bulky primary tumors present. Components of SCC were seen in 23.2% of patients, including the index patient, in whom squamous cell carcinoma was found at the time of preoperative endoscopic biopsy. Glandular elements were reported in 4 patients, and 3 tumors showed carcinoid differentiation [32]. Multiple esophageal carcinomas were reported in 2 patients [22, 30]. Argyrophilia is seen in 15% to 50% of pulmonary oat cell carcinomas [15, 44], and was found in 56% of esophageal SCCs [9-15, 18, 19, 21, 23, 25, 27, 28, 35]. Cytoplasmic argyrophilia is not considered essential for diagnosis [25, 27]. The presence of dense-core granules on electron microscopic examination is important, but not essential for diagnosis [15, 25, 27]. Electron-dense granules characterize SCC of the lung [15, 45], and were found in 66% of esophageal SCCs [10-15, 18-21, 25, 28, 32-35]. The absence of a primary pulmonary SCC was documented in all reported cases of esophageal SCC.

<table>
<thead>
<tr>
<th>Table 1. Tumor Characteristics of Esophageal Small Cell Carcinoma</th>
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<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Upper esophageal lesion (%)</td>
</tr>
<tr>
<td>Midesophageal lesion (%)</td>
</tr>
<tr>
<td>Lower esophageal lesion (%)</td>
</tr>
<tr>
<td>Metastatic at diagnosis (%)</td>
</tr>
<tr>
<td>Associated squamous cell carcinoma (%)</td>
</tr>
<tr>
<td>Mean size of lesion (cm)</td>
</tr>
</tbody>
</table>

* Percent refers to the percentage of affected patients.
Table 2. Treatment Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Mean Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>8</td>
<td>13.1 days</td>
</tr>
<tr>
<td>Surgery</td>
<td>45</td>
<td>8 mo*</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>5</td>
<td>7.8 mo</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>8</td>
<td>4.1 mo</td>
</tr>
<tr>
<td>Surgery + chemotherapy</td>
<td>2</td>
<td>5.5 mo</td>
</tr>
<tr>
<td>Surgery + radiotherapy</td>
<td>1</td>
<td>4 mo</td>
</tr>
<tr>
<td>Surgery + chemotherapy + radiotherapy</td>
<td>1</td>
<td>6 mo</td>
</tr>
<tr>
<td>Chemotherapy + radiotherapy</td>
<td>1</td>
<td>9 mo</td>
</tr>
<tr>
<td>Dilatation</td>
<td>1</td>
<td>1 day</td>
</tr>
</tbody>
</table>

* This excludes 18% operative mortality.

Treatments and Prognosis

Mean overall survival for the 85 patients with evaluable survival data was 5.1 months. For the 64 patients who received some form of treatment, the mean survival was 5.6 months (Table 2). The results of surgical resection as the sole means of treatment were reported for 45 patients, 8 (18%) of whom died perioperatively. Of the 37 surgically treated patients who survived operation, mean survival was 8 months; all deaths were due to widespread metastatic disease. Three patients (8%) were alive at least 2 years after resection [10, 16]. Surgery with adjuvant chemotherapy or radiotherapy, or both, was reported in only 4 patients; survival ranged between 4 and 6 months.

Radiotherapy was the only treatment used in 8 patients with a mean survival of 4.1 months. Chemotherapy, using various drug combinations, was used alone in 5 patients with a mean survival of 7.8 months. One patient treated with a combination of CMC-VAP, ifosfamide, and VP-16 was free from disease at autopsy 11 months later; the patient died of unrelated causes [34]. Another patient survived 9 months after chemotherapy and was receiving radiotherapy for a local recurrence at the time of publication [22]. Chemotherapy appears to give striking remission in most patients for varying lengths of time [17, 19, 26, 34, 35].

The small numbers of patients in each treatment group and the retrospective nature of this review preclude statistical comparisons between treatment groups. The much larger group of patients with pulmonary SCC does afford some historical precedents that may allow us to treat patients with esophageal SCC optimally.

Patients with pulmonary SCC have an approximate 2-year survival rate of 20% when treated with combination chemotherapy [46]. Pulmonary SCC patients also show improved survival when treated with chemotherapy after initial resection [47, 48]. In addition, newer data from several small series [49, 50] show an improved survival in pulmonary SCC patients treated with “salvage” or adjuvant surgical resection after an initial response to systemic chemotherapy. Although only about one third of patients initially treated with chemotherapy are candidates for surgical resection [46], these results are encouraging. The presence of residual tumor in 75% of resected specimens may provide justification for adjuvant surgical intervention [46, 49]. The use of postoperative chemotherapy and thoracic irradiation is also recommended if either nodal disease or residual tumor is present in the resected specimen [46, 51].

The use of prophylactic cranial irradiation in patients with pulmonary SCC is generally recommended because of the 60% to 80% incidence of central nervous system metastases [52, 53]. The incidence of central nervous system metastases in esophageal SCC patients is unknown, although they have been reported in several instances [9, 26, 35]. Careful evaluation of the central nervous system by neurological examination or radiological imaging should be considered in all patients with esophageal SCC and should be followed by cranial irradiation for affected patients [35].

Prospective randomized trials of therapy for esophageal SCC are unlikely given the rarity of the disease. We therefore recommend that patients with such a carcinoma be aggressively evaluated and managed by the surgeon, medical oncologist, and radiation oncologist using lessons learned from treatment protocols for pulmonary SCC. Systemic multidrug chemotherapy should be given either preoperatively or postoperatively, and consideration should be given to mediastinal and cranial irradiation if esophageal lymph nodes reveal metastatic disease.

Conclusion

Esophageal SCC is a rare but rapidly fatal malignancy if untreated. A review of the available data on 130 patients now reported in the literature revealed no optimal treatment protocols, although encouraging results of resection and intense chemotherapy in a few patients exist. Although less than ideal, lessons learned from the treatment of pulmonary SCC may need to be applied to patients with this unusual tumor. A recommendation for multagent chemotherapy either in the preoperative or postoperative setting is warranted. Irradiation should also be used if mediastinal lymph nodes are involved or cranial metastases are present in an effort to salvage as many patients as possible from this lethal disease.

References


