Esophageal Carcinosarcoma: Management and Prognosis at a Single Italian Series

FRANCESCO CA V ALLIN1, MARCO SCARPA1, RITA ALFIERI1, MATTEO CAGOL1, ALBERTO RUOL2, MASSIMO RUGGE3, ERMANNO ANCONA1 and CARLO CASTORO1

1Surgical Oncology Unit, Veneto Institute of Oncology (IOV-IRCCS), Padua, Italy; Departments of 2Surgical Oncological and Gastroenterological Sciences and 3Diagnostic Medical Sciences and Special Therapies, University of Padua, Padua, Italy

Abstract. Background: Esophageal carcinosarcoma (ESC) is a rare malignant lesion of the esophagus with controversial characteristics and prognostic factors. Patients and Methods: Seventeen consecutive patients with esophageal carcinosarcoma were referred to the Center for Esophageal Diseases located in Padua from January 1, 1980 to December 31, 2011. Clinical characteristics, pathological features, treatment and outcome were retrospectively analyzed in a prospectively collected database. Results: Five patients received palliative treatment and one refused surgery; they died of unresected tumor or progression of disease within 0.6-43.5 months after diagnosis. Eleven patients underwent surgical treatment with complete tumor resection; recurrence rate was 80%, leading to death within 2 years after surgery. Only two resected patients are currently alive and free of disease over 20 years after surgery. Conclusion: Our results did not support the better prognosis concept of esophageal carcinosarcoma and suggested the importance of radical esophagectomy with adequate lymph node dissection.

Esophageal carcinosarcoma (ECS) is a rare malignant lesion representing less than 3% of all esophageal neoplasms. It has both carcinomatous and sarcomatous components and Virchow named it after these two components (1). At first, its development was explained by pathologists with the effect of a primary carcinoma on the subsequent malignant growth of the stroma (2).

Further studies have suggested other two hypotheses: the “collision concept” in which both components simultaneously and independently undergo malignant transformation and the “metaplastic hypothesis” in which both components are derived from a single common ancestral cell (3).

In the past twenty years, most articles presented ECS case-report studies that included less than 200 total subjects. Only few studies have retrospectively evaluated local medical databases covering large time spans, in search for patients with a diagnosis of carcinosarcoma (3-8).

ECS patients were mostly found to be males, with a large age interval, and tumor located in the middle third of the esophagus. A favorable prognosis had often been attributed to ECS, mainly based on the concept of the early detection of disease. However, clashing results about prognosis had been reported and this topic remains unclear.

This article includes a series of 17 consecutive cases of esophageal carcinosarcoma presented at our Institute in the past 32 years. The purpose was to shed light on this rare kind of malignancy, in order to provide better patient care.

Patients and Methods

Study design. We retrospectively evaluated all patients presented with esophageal malignancy at the Center for Esophageal Diseases located in Padua from January 1, 1980 to December 31, 2011. Patients’ data were recorded in a prospectively collected database (9), which included patients’ characteristics, tumor features and treatment strategy. Follow-up information, also included in the database, was obtained from scheduled visits.

Of the 5,309 patients included in the database, 17 patients (0.32%) had a diagnosis of ECS and they were included in the study. The clinical and pathological features, including location, tumor size, depth of invasion, metastatic lymph node involvement, were analyzed. Treatment information and outcome data were also included in the analysis.

Staging. Tumor node metastasis (TNM) staging was performed according to the criteria of the International Union Against Cancer (UICC). The sixth edition was used because the most recent carcinosarcoma was diagnosed before 2010 (10). Pretreatment
evaluations for esophageal carcinosarcoma, as well as other esophageal cancer histotypes, included barium tests, esophageal endoscopy, computed tomography (CT) of the neck, chest, and abdomen, as well as bronchoscopy. Endosonography (EUS) of the esophagus has been part of our routine esophageal cancer staging since 2000 and positron emission tomography scan since 2005.

Surgical treatment. The surgical technique has already been published elsewhere (11). Esophagectomy was performed using an Ivor-Lewis procedure via a laparotomy and right thoracotomy for tumors located in the mid-lower esophagus and esophagogastric junction. A 3-stage procedure, with an additional left cervical incision, was performed in tumors of the upper third of the esophagus. A pharingo-laringo esophagectomy was reserved to cervical esophageal tumors involving the upper esophageal sphincter. En bloc lymph node dissection was routinely performed: in cervical tumors cervical nodes were resected. The alimentary tract was reconstructed using the gastric pull-up technique. Patients were examined at regularly scheduled intervals by members of the surgical team after 1, 3, 6 and 12 months and every 6-12 months thereafter.

Statistics. Patients’ data were collected in Microsoft Access database and exploratory statistical analysis was performed using the SAS 9.1 software. Categorical data were expressed as number and percentage, continuous data as median and interquartile range (IQR).

Results

Patients’ characteristics. Seventeen patients (0.32% among all esophageal malignancies reported at our Institution) had a diagnosis of ECS in the specific study period. Patients’ characteristics are shown in Table I. Most of them were males (88.2%) with a median age of 62 years (IQR=60-69). The most common tumor sites were the middle thoracic esophagus (7/17, 41.2%) and the cervical esophagus (6/17, 35.3%). The median tumor length was 55 mm (IQR=40-70). Twelve patients (70.5%) had clinical stage I-II at diagnosis. With regard to depth of invasion, three were superficial (T1), four involved the muscularis propria (T2), eight involved the adventitia (T3) and two involved the adjacent structure (T4). Lymph node metastasis was diagnosed in 5 patients (29.4%) and one (5.9%) had distant metastases.

Pathological features. Pre-treatment evaluations for ECS were performed as described in the Patients and Methods section. Upon macroscopic evaluation, 14 patients (82.4%) had polypoid tumors and 3 (17.6%) had ulcerative tumors. Microscopic examination identified two tumor components, carcinomatous cells and sarcomatous cells. The carcinomatous elements were squamous cell carcinoma in 16 patients and anaplastic in one patient. The sarcomatous elements were spindle cell carcinoma in 16 patients and anaplastic in one patient. The sarcomatous elements were spindle cell sarcoma in all patients.

Treatment and clinical outcome. Treatment strategies are shown in Table II. One patient (cT2N0M0) refused surgical treatment and he died at 14 months from diagnosis because of disease progression. Five patients received endoscopic treatment due to poor conditional status or clinical M1 stage. Three of them received endoscopic palliation (laser therapy or endoscopic stenting) and they died at 2, 22 and 43 months after treatment because of disease progression; 2 patients received definitive gastrostomy and they died within 6 months after treatment because of the progression of the disease.

Eleven patients underwent radical surgery with complete tumor resection (R0): esophagectomy in 9 and pharingo-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Tumor site</th>
<th>Tumor length (mm)</th>
<th>Clinical stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>50</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>2</td>
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<tr>
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</tr>
<tr>
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<td>60</td>
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<tr>
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<td>50</td>
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</tr>
<tr>
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<td>100</td>
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<tr>
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<tr>
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<tr>
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<td>Female</td>
<td>Cervical esophagus</td>
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<td>T1N0M0</td>
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laringo esophagectomy in 2. One of them died of postoperative complications (myocardial infarction) and 8 patients died of tumor recurrence within 2 years after surgery (range=3.5-22 months). The recurrence was local in one patient, distal in 2 patients and both in 5 patients. Only 2 patients are alive “free of disease” at 291 and 314 months after surgery.

Clinical stage and pathological stage of patients who underwent resection without neoadjuvant therapy are shown in Table III. Depth of tumor invasion was correctly diagnosed in 4/10 (40%), lymph node involvement in 6/10 (60%) and clinical M stage in 10/10 (100%).

Metastatic lymph node distribution. After histopathological examination of all resected specimens, lymph node metastasis was found in 7 out of 11 patients (63.6%) who underwent surgical treatment. The most involved node was the paraesophageal node (34.4%) followed by laterocervical, subcarinal, recurrent nerve and paracardial ones (18.2%). Paratracheal, inferior pulmonary vein and perigastric nodes was less frequently involved (9.1%).

Discussion

The low incidence of ECS limits the available information on this kind of malignancy. The literature reports a rate less than 3% of all esophageal malignancy, thus most studies were case-reports with limited investigatory resources (12-17). Only centers with high volume and long time experience could report more than one or two ECS patients (3-5).

However, information from case reports could be gathered to gain understanding of disease features. A summarizing effort was performed by Iascone et al. in 1999, collecting a total of 127 carcinosarcomas and 57 pseudosarcomas from the literature (18). In 2006 Sanada et al. reviewed 57 cases of ECS reported in Japan between 1995 and 2004 (17). Both reviews allowed for exploration of ECS characteristics and they showed a wide age interval (between 44 and 86 years after surgery).
old), the predominant male gender (over 80%), the main tumor location in the middle third of the esophagus (over 50%) and early stage at diagnosis (invasion to, but not beyond the, submucosa in almost half of the patients). Our data confirmed the wide age interval, the male predominance and the middle third of esophagus as the main tumor location. Few patients had superficial ECS (17.7%), as reported also by Wang et al. (24%) (3) and Kuo et al. (27%) (4). These data clashed with the higher rate (from 40% to 80%) shown in older studies (7, 15, 16) and by Zhang et al. (8).

Although the limited esophageal wall penetration, a considerable involvement of regional lymph nodes has been reported since the first reviews (17, 18), confirmed by later single-Institution studies. (3, 4, 5) Lymph node metastasis was found in over 60% of our patients who underwent surgical resection.

The main curative treatment for ECS is esophagectomy, with a surgical rate between 75% and 95% (3, 4, 17,18). However, poor conditional status or clinical M1 stage prevented 29.4% of patients in our sample from surgical resection, influencing their prognosis. The role of neoadjuvant therapy is still unclear since the early stage at diagnosis drives clinicians to first-line surgery and prevents researchers from exploring this facet. Our data, thus, cannot be useful because only one patient received neoadjuvant therapy.

A better prognosis had often been attributed to ECS with respect to other esophageal malignancy. Some researchers supported this concept suggesting the underlying effect of the intraluminal growth on the early detection of the disease. Thus, the growth would have affected the early onset of symptoms, resulting in prompt diagnosis and lower propensity for tumor invasion (16, 19).

Actually, clashing results about prognosis have been reported. Two recent retrospective Chinese studies showed quite good prognosis for their patients, with a 3-year overall survival over 50% and 5-year overall survival over 40% (3, 8). An older Chinese paper described four patients who were all alive “free of disease” after 3 years of surgical resection (19) and a Japanese study reported a 3-year overall survival of 62.8% (that dropped to 26.7% at 5 years) (7). The concept of better prognosis was not supported by two recent Japanese studies that reported a similar prognosis for ECS patients and esophageal squamous cell carcinoma patients. Kuo et al. suggested a relationship between early lymphatic spreading, distant metastasis and poor prognosis (4). Sano et al. reported an even lower survival in ECS T1 patients than in esophageal squamous cell carcinoma T1 patients (5). Both reviews reported a poor prognosis in their pools of ECS patients (17, 18). In a 2006 review, only 13% of resected patients were reported to be alive “free of disease” at 2 years after surgery (17) In a 1999 review, the rate of resected patients alive “free of disease” or dead from unrelated causes dropped from about 60% at 3 years after surgery to about 15% at 5 years (18). In our cases, 29.4% of resected patients did not undergo surgical resection and only 18.2% were alive “free of disease” at 2 years after surgery.

This study has some limitations mainly due to the rarity of the malignancy— that are common among similar studies. It is a single-Centre retrospective study and includes a limited number of patients. It also covers an extended time period, leading to possible bias related to changes in diagnostic procedure and in treatment strategies.

Conclusion

Our results did not support the better prognosis concept of ECS and suggested the importance of radical esophagectomy with lymph node dissection, followed by careful follow-up monitoring of lymph nodes. The role of neoadjuvant therapy remains unclear and further data are required to explore the possible benefits in curative treatment of this malignancy. In addition, since the low incidence of ECS prevents researchers from gathering adequate-sized samples, more information could be provided by retrospective explorations of single-Center experience.

Funding

This study was supported by Current Research Fund from the Italian Ministry of Health to Carlo Castoro.

Conflicts of Interest

The Authors declare no conflicts of interest.

References


