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What is This?
Pattern of Failure in Surgically Treated Patients with Cervical Esophageal Squamous Cell Carcinoma

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Abstract

Objective. The aim of this study was to analyze the pattern of failure in patients who have undergone surgical resection for cervical esophageal squamous cell carcinoma.

Study Design. Case series with chart review.

Setting. University hospital.

Subjects and Methods. Sixty-two patients who had undergone surgical resection of cervical esophageal squamous cell carcinoma from January 2001 through April 2012. Sites of failure were documented.

Results. Twenty-nine patients had developed treatment failure. Of the 29 patients, 14, 13, and 14 had developed local failure, regional failure, and distant metastasis, respectively. Of the 13 regional failures, the images of 2 patients were lost. The other 11 regional failures included left lateral nodal disease at level II (n = 2), level III (n = 4), and level IV (n = 7); right lateral nodal disease at level II (n = 2), level III (n = 3), and level IV (n = 3); and level VI (n = 4). The overall 2-year local failure–free survival rate and regional failure–free survival rates were 79.6% and 58.6% (P = .04) for patients with stage II disease and 79.6% and 59.6% (P = .054) for patients with stage III disease, respectively.

Conclusions. The pattern of failure of cervical esophageal squamous cell carcinoma is characterized by early locoregional failure, especially in patients with stage III disease.

Keywords

cervical esophageal squamous cell carcinoma, pattern of failure, surgery, treatment, survival

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Cervical esophageal squamous cell carcinoma is relatively uncommon, representing less than 5% of all esophageal cancer.1 The management of cervical esophageal cancer is controversial. The choice of treatment has been surgical resection,2-5 radiation therapy,6-11 or a combination of the two. Accurate knowledge of the temporal, anatomical, and biological pattern of failure following surgery has important implications for planning therapeutic strategies. The purpose of this study is to analyze the pattern of failure in patients who have undergone surgical resection for cervical esophageal squamous cell carcinoma.

Methods

Patients and Patient Workup

The Case Recording System was approved by an independent ethics committee (Cancer Hospital, Chinese Academy of Medical Sciences) to identify the patients diagnosed with cervical esophageal squamous cell carcinoma in our center from January 2001 through April 2012. From 2001 through 2012, a total of 64 patients with cervical esophageal squamous cell carcinoma received surgical resection and 2 patients were excluded from this study for nonregional lymph nodal metastases. Of the 62 patients, 35 received postoperative radiotherapy. The pretreatment workup included a complete history and physical examination, liver and renal biochemistry, complete blood count, barium contrast study, endoscopy, computed tomography (CT) scans of the neck and thorax, and ultrasonography of the abdominal region and the cervical region with or without fine-needle aspiration cytology when cervical nodal metastasis was detected. Endoscopic ultrasonography and positron emission tomography fusion with CT scans have been available since
September 2007. In addition, bronchoscopy was performed for patients with local advanced diseases unless the patient’s condition was not suitable or when the patient declined. The new seventh edition of the Union for International Cancer Control–American Joint Committee on Cancer (UICC-AJCC) TNM staging system for esophageal cancer is based only on pTNM from esophageal cancers treated by esophagectomy alone. Thirty-five patients received postoperative radiotherapy in this study, and primary radiotherapy was given to patients with cervical esophageal cancer in some centers. Therefore, all patients underwent disease staging using the UICC-AJCC 2002 staging system in this study.

Surgery

Pharyngo-laryngo-esophagectomy was performed by first mobilizing the esophagus using a transhiatal or thoracoscopic approach. The larynx, pharynx, and cervical esophagus were resected. Open laparotomy was used for the abdominal phase of the operation. The stomach or the free jejunal transplant was the conduit of choice to restore gastrointestinal continuity. Selective neck dissection was performed for all patients.

Postoperative Radiotherapy

Patients with cervical esophageal squamous cell carcinoma receiving primary surgery with 2 or more involved nodes, positive margins, extracapsular nodal spread of tumor, classification T3-4, or histologic grade 3 were given postoperative radiotherapy unless the patient’s condition was not suitable or when the patient declined in our center. Among the 35 patients with postoperative radiotherapy, 22 were irradiated using conventional techniques by anteroposterior opposing fields or oblique fields at a daily dose of 2 Gy, whereas 13 were treated using intensity-modulated radiation therapy at a daily dose range of 1.8 to 2.0 Gy to the planning target volume. The median dose of postoperative radiotherapy was 50 (range, 45-60) Gy. The field of radiation covered the tumor bed with an additional radial margin of at least 1 cm and longitudinal margin of at least 3 cm. Adjacent region of positive lymph nodes was included in the radiation field. The median time from surgery to day 1 of postoperative radiotherapy was 8 (range, 3.14-13) weeks. Two patients received concurrent chemotherapy with cisplatin administered weekly (30 mg/m²) and every 3 weeks (80 mg/m²), respectively.

Treatment Monitoring

All patients were required to be followed up after the completion of treatment: 1 month after the completion of treatment, every 3 months in the first 2 years, every 6 months from years 3 through 5, and annually thereafter. Each follow-up included a complete examination, including basic serum chemistry, barium contrast study, and ultrasonography of the abdominal region and the cervical region. Computed tomography scans of the neck and thorax and endoscopy were performed after the completion of treatment and then every 6 months.

Definition of Failure Pattern Terms

The records of all patients were reviewed to assess the site or sites of treatment failure. Failure patterns were classified as local, regional, or distant. Category was determined at the time of last follow-up. Local failure refers to failure of the primary tumor. Regional failure is defined as recurrence in regional lymph nodes. Distant failure is defined as the appearance of a tumor at a site representing hematogenous dissemination.

Statistical Analyses

SPSS version 17.0 (SPSS, Inc, an IBM Company, Chicago, Illinois) was used for statistical analysis. The local failure–free survival (LFFS), distant failure–free survival (DFFS), regional failure–free survival (RFFS), and overall survival (OS) were estimated by use of the Kaplan-Meier method. The LFFS, DFFS, RFFS, and OS were measured from day 1 of treatment to the date of the event. Statistical tests were based on a 2-sided significance level. P < .05 was considered to indicate statistical significance.

Results

Survival Rates

There were 10 female and 52 male patients with an age range of 24 to 73 years (median age, 57.5 years); 29 patients had stage II disease and 33 had stage III disease. Seven patients had synchronous multiple primary carcinoma, and 8 had metachronous multiple primary carcinoma. The median follow-up time was 13.3 months. For all patients, the overall 2-year LFFS, RFFS, DFFS, and OS rate was 68.3%, 69.5%, 62.3%, and 50.5%, respectively (Figure 1). The overall 2-year LFFS rate for patients treated with surgery and patients treated with surgery plus postoperative radiotherapy was 75.5% and 64.5%, respectively (P = .90). The median local failure time for patients treated with surgery and patients treated with surgery plus postoperative radiotherapy was 3.5 months and 7.8 months, respectively. The overall 2-year RFFS rate for patients treated with surgery and patients treated with surgery plus postoperative radiotherapy was 49.4% and 81.7%, respectively (P = .03). The overall 2-year LFFS rate for patients with stage II and stage III disease was 79.6% and 58.6%, respectively (P = .04). The overall 2-year RFFS rate for patients with stage II and stage III disease was 79.6% and 59.6%, respectively (P = .054). The overall 2-year OS rate for patients with stage II and stage III disease was 69.6% and 32.0%, respectively (P = .003).

Pattern of Failure

At their last follow-up visit, 29 patients had developed treatment failure. Of the 29 patients, 14, 13, and 14 had developed local failure, regional failure, and distant metastasis, respectively. The details of the 29 patients with treatment failure are shown in Figure 2.
Of the 13 regional failures, the images of 2 patients were lost. The other 11 regional failures included left lateral nodal disease at level II (n = 2), level III (n = 4), and level IV (n = 7); right lateral nodal disease at level II (n = 2), level III (n = 3), and level IV (n = 3); and level VI (n = 4) according to consensus guidelines. The metastatic sites included the lung in 8, the bone in 3, the liver in 2, the subcutis in 2, the pleura in 2, the mediastinal lymph nodes in 3, and other distant lymph nodes in 2 patients. The median time to local failure was 6.8 (range, 2.5-23.0) months, except 1 patient who was treated in February 2012 and had local failure after 20 days for invading trachea. The median time to regional failure was 7.1 (range, 1.87-22.8) months. The median time to distant metastasis was 14.1 (range, 1.87-26.9) months.

Discussion

Natural and surgically manipulated pathways of tumor spread determine subsequent patterns of failure. In cervical esophageal squamous cell carcinoma, direct extension can lead to local failure, lymphatogenous spread to regional failure, and hematogenous spread to failure at distant sites. Triboulet et al reported that 209 patients with locally advanced tumors of the hypopharynx (n = 131) or cervical esophageal carcinomas (n = 78) underwent total pharyngolaryngectomy with visceral interposition. After a mean follow-up time of 28.5 months, tumor recurrences occurred in 118 patients (59.3%) with a mean delay of 19 months (range, 1-104 months). Local recurrence alone occurred in 46 patients and was combined with neck recurrence in 48 patients. Distant metastases were found in 22 patients, and 2 patients had tumor recurrences at unknown sites. Our results are different from the study by Triboulet et al probably because of the advance of the diagnostic workup. These diagnostic workups such as PET-CT and endoscopic ultrasonography were performed for patients with cervical esophageal squamous cell carcinoma in this study.

There is clearly likely to be considerable overlap between local and regional failure due to the difficulty in distinguishing lymph node groups on a CT scan, and the categorization in this study into local failure, regional failure, and distant metastasis is somewhat artificial. Also, it was difficult to define regional failure for some patients with thoracic esophageal extension and mediastinal lymph nodes metastases or multiple primary carcinoma. Among the 13 patients with regional failure, 3 had multiple primary carcinoma and 3 had thoracic esophageal extension.

In 1908, Butlin described an operation that we would now call selective neck dissection to remove cervical lymph nodes in cancer of the tongue. Many surgeons employ selective neck dissection for the initial management of the neck in patients who have no clinical evidence of lymph node metastasis and in selected patients with clinically positive lymph nodes. In terms of esophageal cancer, there has also been much debate regarding what constitutes an adequate lymph node dissection during esophagectomy. No significant difference in 5-year survival was found between the

![Figure 1](http://example.com/figure1.png)

**Figure 1.** Kaplan-Meier curve showing overall survival (OS), local failure-free survival (LFFS), regional failure-free survival (RFFS), and distant failure-free survival (DFFS) of patients with cervical esophageal squamous cell carcinoma in the study.

![Figure 2](http://example.com/figure2.png)

**Figure 2.** Details of the 29 patients with treatment failure are shown.
transhiatal esophagectomy group and the transthoracic esophagectomy group in this prospective randomized study. In addition, 3-field esophagectomy techniques have been associated with increased morbidity, particularly recurrent laryngeal nerve injury, which has been reported in up to 9%. Selective neck dissection was performed for all patients in our study, and no patients developed regional failure at level I or level V.

The RTOG 9501 trial and the EORTC 22931 trial indicated that extracapsular nodal spread, positive surgical margins, multiple positive nodes, vascular/lymphatic/perineural invasion, and pT3 or pT4 primary tumor were indications for postoperative radiotherapy in patients with head and neck cancer. Also, postoperative prophylactic radiotherapy improved the 5-year survival rate in patients with thoracic esophageal cancer who had positive lymph node metastases and in patients with stage III disease in this prospective study of esophageal carcinoma from our center. However, cervical esophageal squamous cell carcinoma was not included in these studies. In the study by Triboulet et al, which included 78 patients with cervical esophageal cancer, multivariate analysis indicated that postoperative radiotherapy was a strong prognostic factor of OS. In our study, postoperative radiotherapy prolonged the median local failure time and improved the regional control for patients with cervical esophageal squamous cell carcinoma.

The optimal postoperative radiotherapy target volume for cervical esophageal squamous cell carcinoma is disputed. Tong et al reported that postoperative radiotherapy target volume included the tumor bed and the relevant drainage areas. The field of radiation covered the tumor bed with an additional radial margin of at least 1 cm and a longitudinal margin of at least 3 cm, and an adjacent region of positive lymph nodes was also included in our center. Our study indicated that the tumor bed, with bilateral levels II, III, IV, and VI, should be included in the postoperative radiotherapy field. In addition, the postoperative dose was often compromised by limitations imposed by the stomach or the free jejunal transplant. Concurrent chemotherapy or targeted therapy might be used to improve the efficiency of postoperative radiotherapy.

Conclusions
The pattern of recurrence of cervical esophageal squamous cell carcinoma is characterized by early locoregional failure, especially in patients with stage III disease. Further research is required to better identify adjuvant radiotherapy or chemoradiotherapy in the treatment of this cancer.

Author Contributions
Cai-Neng Cao, conception and design, analysis and interpretation of data, drafting the article, final approval of the version to be published, agreement to be accountable for all aspects of the work; Shao-Yan Liu, drafting the article, final approval of the version to be published, acquisition of data, agreement to be accountable for all aspects of the work; Jing-Wei Luo, conception and design, analysis and interpretation of data, drafting the article, final approval of the version to be published, agreement to be accountable for all aspects of the work; Li Gao, analysis and interpretation of data, final approval of the version to be published, revising the article critically for important intellectual content, agreement to be accountable for all aspects of the work; Guo-Zhen Xu, analysis and interpretation of data, drafting the article, final approval of the version to be published, agreement to be accountable for all aspects of the work; Zhen-Gang Xu, drafting the article, final approval of the version to be published, acquisition of data, agreement to be accountable for all aspects of the work; Ping-Zhang Tang, conception and design, final approval of the version to be published, revising the article critically for important intellectual content, agreement to be accountable for all aspects of the work.

Disclosures
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