

# Predictors of Survival After Treatment of Oligometastases After Esophagectomy

Galal Ghaly, MD, Sebron Harrison, MD, Mohamed K. Kamel, MD, Mohamed Rahouma, MD, Abu Nasar, MS, Jeffrey L. Port, MD, Brendon M. Stiles, MD, and Nasser K. Altorki, MD

Division of Thoracic Surgery, Department of Cardiothoracic Surgery, New York Presbyterian Hospital, Weill Cornell Medical College, New York, New York

**Background.** Recurrent esophageal carcinoma (EC) has a dismal prognosis. However, prior studies showed that selected patients with isolated recurrence may benefit from definitive therapy. The aim of this study was to identify the predictors of postrecurrence survival (PRS) in patients with isolated EC recurrence who were treated with curative intent.

**Methods.** A retrospective review of a prospective database (1988 to 2015) was performed to identify all recurrent EC patients after curative esophagectomy. Demographic and clinicopathologic data were reviewed. The probability of PRS was estimated with the Kaplan-Meier method. Predictors of PRS after definitive therapy for isolated EC recurrence were determined by the multivariable Cox proportional hazards model.

**Results.** Of the 640 curative esophagectomies, 241 patients (37.7%) experienced recurrences (median follow-up 50 months). Fifty-six patients (9%) received definitive

treatment of isolated EC recurrence (31 were treated surgically with or without chemotherapy-radiotherapy [CTRT] and 25 received definitive CTRT alone). Median time to recurrence (TTR) was 19 months. The 1- and 3-year PRSs were 78% and 38% (median survival 26 months). On multivariable analysis; TTR was the only significant independent predictor for survival after recurrence (hazards ratio 0.98, 95% confidence interval: 0.96 to 0.99,  $p = 0.034$ ). No pronounced difference was found in disease-free survival or in PRS between recurrent patients treated with operation with or without CTRT and patients who received definitive CTRT.

**Conclusions.** A select subgroup of patients with isolated EC recurrence can be treated with curative intent. TTR was the best predictor for PRS.

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Esophageal cancer (EC) is a highly lethal malignancy responsible for nearly 16,000 deaths in the United States in 2015 [1]. The management of EC has undergone major evolutions over the past 15 years, particularly the introduction of multimodality treatment regimens. Despite that, approximately one-half of the patients experience cancer recurrence after curative esophagectomy [2–6]. Most recurrences occur in the first postoperative year, and approximately 90% develop by the end of the third year [2]. Patients who experience locoregionally recurrent or metastatic disease are usually referred for systemic therapy (with or without local therapy) with palliative intent. However, potentially curative, definitive, treatment of a limited number of cancer metastasis has historically been performed on an individual patient basis [7–9]. The concept of oligometastases was initially proposed by Hellman [10] in 1995 as a

midway in a continuum from localized to widespread disease and is thought to represent a variant of metastatic disease that is perhaps more indolent in clinical and biological behavior. The clinical implication of oligometastasis lies largely in the improved disease control, survival, and even cures noted when oligometastatic disease is treated with definitive local therapy. This improved disease control has been reported in different types of malignancies, including colorectal, kidney, and non-small cell lung cancer. Most studies vary in the number of metastatic lesions considered to represent oligometastases, although the common range is one to five lesions [11].

In 2003 Mao and colleagues [12] published a case report on the successful outcome of definitive treatment for two sites of visceral metastasis after esophagectomy. However, to our knowledge, the role of definitive therapy in the setting of oligometastatic EC has not been more thoroughly investigated. We have previously reported on 27 patients who were definitively treated for localized metastatic disease after esophagectomy. Few anecdotal reports on the management of isolated EC recurrences and postrecurrence oncologic outcomes currently exist.

In this study we sought to identify the frequency and to evaluate treatment modalities of isolated EC recurrences

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Address correspondence to Dr Altorki, Department of Cardiothoracic Surgery, Ste M404, Weill Medical College of Cornell University, 525 E 68th St, New York, NY 10021; email: [nkaltork@med.cornell.edu](mailto:nkaltork@med.cornell.edu).

after esophagectomy. In addition, we sought to explore predictors of postrecurrence survival in patients who had received definitive treatment of the isolated EC recurrence.

## Patients and Methods

### Study Design

We conducted a retrospective review of a prospectively assembled thoracic surgery database. The Institutional Review Board of Weill Cornell Medicine and the New York Presbyterian Hospital approved the database and study design. Patient consent was waived. Patients considered eligible for study had undergone curative (R0) esophagectomy for EC between 1988 and 2015 and had subsequently experienced disease recurrence. Patients with isolated (single) site of recurrence and amenable for definitive treatment were included. Sites of recurrence included both locoregional as well as distant disease, as long as these were the only sites of recurrent disease. Patients with multiple distant metastasis or locoregional recurrence not amenable to definitive treatment were excluded from the study. Hospital and office records were reviewed for demographic, clinical, and pathologic variables, including age, sex, and performance status (PS). Histologic cell type, use of neoadjuvant or adjuvant therapy, and pathologic stage of the primary tumor were included in the analysis. Comorbidities were measured by Charlson Comorbidity Index (CCI). Further details on specific site of recurrence, type of treatment of recurrence, disease-free interval, and survival after recurrence were also included. Staging of the primary EC was assigned according to the TNM classification of the American Joint Committee for Cancer Staging (seventh edition).

### Follow-Up

After hospital discharge, patients were seen at 3-month intervals for the first 12 months, followed by every 6 months up to year 3, and finally annually thereafter. Computed tomography (CT) scans of the chest and upper abdomen were done postoperatively every 6 months for 3 years and annually thereafter. Other studies, such as endoscopy and positron emission tomography (PET) scanning, were done only if clinically indicated. All data were collected, entered into a prospective database, and updated at regular intervals until the patient's last follow-up or death. The same follow-up plan was implemented after treatment of any recurrence.

### Recurrence

Locoregional recurrence was defined as a recurrence that developed at the anastomotic site or nodal recurrence within the previously dissected nodal basins, including the cervical, mediastinal, or upper abdominal area. Distant recurrence was defined as hematogenous metastasis to solid organs, pleura disease, or recurrence at nodal sites outside of the prior resection bed. Simultaneous locoregional and distant recurrences were

classified as combined recurrence [3, 4]. Recurrences were considered isolated if the patient had single site of recurrence confined to a local anastomotic/gastric recurrence or a single node/nodal station or a solitary distant site [5]. Diagnosis of recurrent disease was based on histologic evaluation or definite radiologic findings. All patients underwent CT scanning of the chest and upper abdomen, endoscopic evaluation for intraluminal disease, and PET scanning to confirm the solitary nature of the recurrence. Recurrent patients treated with definitive therapy were divided into two further groups: surgically treated group (n = 31) versus definitive chemotherapy-radiotherapy (CTRT) group (n = 25).

### Statistical Analysis

The database was queried to identify relevant clinical and pathologic characteristics, which were represented by descriptive statistics (frequency and percentage, median, and interquartile range). Cox proportional hazards regression analysis was performed to identify predictors of survival for definitively treated recurrent EC patients after curative esophagectomy. Univariate analysis examined age, sex, PS, CCI, neoadjuvant therapy, extent of resection of primary tumor, pathologic T class, pathologic N class, histologic cell type, histologic grade, time to recurrence, and type of treatment of recurrence. Univariate predictors with probability values less than 0.20 were included in the multivariable model. Collinearity between potential predictors was examined (using the Kappa statistic) before the final multivariable model was formulated. In the multivariable model, predictors with a *p* value equal to or less than 0.05 were deemed significant predictors. Survival probabilities were estimated using the Kaplan-Meier method. The log-rank test was used to determine significance of survival distributions among groups. The postrecurrence survival was defined as the interval between the detection of initial recurrence and either death or the last follow-up. The receiver operating characteristic (ROC) curve was used to determine the cutoff of time to recurrence effect on postrecurrence survival. Data analysis was performed with IBM SPSS software version 22.0 (SPSS, Inc, Chicago, IL).

## Results

### Patient Characteristics

A total of 641 consecutive patients were treated with R0 esophagectomy between 1988 and 2015, and 241 of the patients (37.7%) experienced recurrent disease. Twenty-six patients with oligometastasis received palliative chemotherapy because of their poor PS. Fifty-six patients with oligometastasis were treated with curative intent by surgical resection (with or without chemoradiation) or definitive CTRT were included in our final analysis. Forty-seven of the 56 patients (84%) included in this study had locally advanced disease ( $\geq$  stage 2) at the time of the index operation, and none of them had oligometastatic disease at presentation.

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