# Surgical Resection of Rare Esophageal Cancers

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*Background.* **Although surgical resection of adenocarcinoma or squamous cell carcinoma of the esophagus is standard practice, the treatment strategy for other malignant rare esophageal cancers is still under debate. The aim of this study was to examine the treatment of rare malignant esophageal cancers and to evaluate the survival of these patients.**

*Methods.* **A retrospective review of all esophagectomies performed at Mayo Clinic from 1980 to 2014 (approximately 4,000 cases) identified 24 patients with histologic features other than adenocarcinoma or squamous cell carcinoma. Their medical records were reviewed for demographics, presenting symptoms, evaluation, surgical management, pathologic features, and short-term and long-term outcome.**

*Results.* **Pathologic identifications included small cell carcinoma, lymphoma, and undifferentiated carcinoma in 4 (16.7%) patients each and neuroendocrine, melanoma, leiomyosarcoma, sarcomatoid, sarcoma, and gastrointestinal stromal tumor in 2 (8.3%) patients each. The most common presenting symptoms included dysphasia in 91.7% patients (22/24), pain in 75.0% (18/24), and weight loss in 62.5% (15/24). Preoperative evaluation included barium swallow in 91.7% (22/24), computed tomography in 91.7% (22/24), positron emission tomography in 54.2% (13/24), esophagogastroduodenoscopy in 100% (24/24), and endoscopic ultrasonography in 29.2% (7/24) patients. The location of the tumor was at the gastroesophageal junction in 41.7% (10/24). There was no operative mortality, and 13 patients (54.16%) had at least one postoperative adverse event. The 1-year survival after esophagectomy was 69.7%, the 5-year survival was 42.7%, and the 10-year survival was 37.4%.**

*Conclusions.* **Esophageal cancer with pathologic features other than squamous cell carcinoma or adenocarcinoma is rare. Esophagectomy for rare types of malignant esophageal cancers should be considered part of the effective treatment paradigm.**

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Esophageal cancer is diagnosed in approximately 18,000 Americans a year [1]. The majority of these esophageal cancers will be adenocarcinoma or squamous cell carcinoma, both having well-established treatment and staging paradigms. Only 3% to 4% of esophageal cancers will be other rare malignant pathologic features of the esophagus, including small cell carcinoma, melanoma, sarcoma, and lymphoma. The current literature on rare esophageal cancers is mainly composed of case reports or very small case series, demonstrating that there is a great need for information about these diseases [2]. Interestingly, the presenting symptoms of rare esophageal cancer are similar to those of squamous cell carcinoma and adenocarcinoma of the esophagus, but the treatment is not well established at this time. This study examined the Mayo Clinic's surgical experience with rare esophageal cancers.

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## Patients and Methods

### *Data Collection*

The Mayo Institutional Review Board approved a retrospective study to collect data including demographics, presenting symptoms, evaluation, surgical management, pathologic features, and short-term and long-term outcome for patients who had an esophagectomy from 1980 to 2014 (Table 1). Patients with carcinoma of the esophagus other than adenocarcinoma and squamous cell carcinoma were included in the study, totaling 24 patients. All surviving patients were followed up with standard postoperative visits and telephone calls until October 2014.

### *Statistics*

The descriptive statistics for discrete variables are reported as number and percentage. For continuous variables the median and range or mean and standard deviation are reported as appropriate. The primary outcome of patient survival was estimated by the Kaplan-Meier survival method. Univariate associations of variables with patient survival were assessed by Cox models, and the results are reported as hazard ratio (HR) and 95%


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*Table 1. Patient Characteristics*

| Characteristic | Total (N = 24) |
|---|---|
| Sex | |
| F | 7 (29.2%) |
| M | 17 (70.8%) |
| Age | |
| N | 24 |
| Mean (SD) | 62.1 (12.1) |
| Median | 61.7 |
| Q1, Q3 | 56.3, 70.2 |
| Range | (33.1–83.6) |
| Procedure | |
| Ivor Lewis | 16 (66.7%) |
| Left thoracoabdominal | 1 (4.2%) |
| McKweon | 2 (8.3%) |
| Transhiatal | 4 (16.7%) |
| Extended Ivor Lewis with colon interposition | 1 (4.2%) |
| Previous smoker | |
| No | 12 (50.0%) |
| Yes | 12 (50.0%) |
| Postoperative chemotherapy | |
| No | 14 (58.3%) |
| Yes | 10 (41.7%) |
| Postoperative radiation | |
| No | 19 (79.2%) |
| Yes | 5 (20.8%) |

SD = standard deviation.

confidence interval (CI). The α-level was set at 0.05 for statistical significance.

## Results

### *Preoperative Assessment*

A retrospective review of 4,000 esophagectomies performed at Mayo Clinic from 1980 to 2014 identified 24 patients with esophageal cancer with histologic features other than adenocarcinoma or squamous cell carcinoma. The median age of the patients was 62.1 years (range, 33.1 to 83.6 years). The majority of the patients were men (n = 17, 70.8%), and 7 (29.2%) were women (Table 1). The most common presenting symptoms included dysphasia, which occurred in 22 (91.7%) patients, pain in 18 (75.0%) patients, and weight loss in 15 (62.5%) patients. Half of the patients were smokers and half were nonsmokers.

The preoperative evaluation included a barium swallow in 22 patients (91.7%), computerized tomography (CT) in 22 (916%), positron emission tomography (PET) in 13 (54.2%), esophagogastroduodenoscopy in all 24 (100%), and endoscopic ultrasonography in 7 (29.2%). The tumor was located at the gastroesophageal junction in 10 patients (41.7%), the distal esophagus in 10 (41.7%), and the mid-esophagus in 4 (16.7%). Before operation, 3 patients received neoadjuvant therapy, 1 patient received both chemotherapy and radiation, 1 patient received chemotherapy alone, and 1 patient received radiation alone.

### *Surgical Approach and Final Pathologic Indentification*

The most frequently performed esophageal operation was an Ivor Lewis esophagogastrectomy in 16 (66.7%) patients, a transhiatal esophagectomy in 4 (16.7%), a McKweon procedure in 2 (8.3%), and a left thoracoabdominal esophagogastrectomy and an extended Ivor Lewis procedure with colon interposition in 1 (4.2%) patient each (Table 1). The average hospital stay was 19.5 days (range, 7 to 51 days). There was no operative mortality. Thirteen patients (54.2%) had at least one postoperative adverse event. The most common adverse events included anastomotic leak, seen in 5 patients (20.8%), and pneumonia, which occurred in 7 patients each (29.2%).

A wide variety of pathologic conditions were identified (Table 2). The most common were small cell carcinoma, lymphoma, and undifferentiated carcinoma in 4 patients each. Neuroendocrine, melanoma, leiomyosarcoma, sarcomatoid, gastrointestinal stromal tumor (GIST), and sarcoma were identified in 2 patients each.

### *Follow-Up and Survival*

The Patients were seen for follow-up with computed tomography at standard postoperative intervals. They were followed up by phone call until October 2014 to confirm status and survival. Follow-up was completed in 23 of 24 patients (95.8%). The median follow-up time was 15.1 years, with 1 patient lost to follow-up at hospital discharge to a maximum of 18.8 years. The overall median survival was 3.2 years (Fig 1, Table 3). One patient was lost to follow-up. The 1-year survival after esophagectomy was 69.7%, the 5-year survival was 42.7%, and the 10-year survival was 37.4% (Table 3). Postoperative chemotherapy or radiation therapy was given to 13 (54.2%) patients and was not significantly associated with increased survival (Table 3).

## Comment

Because of the small number of patients and the variety of pathologic features identified in this group of patients, it is difficult to demonstrate statistically significant conclusions regarding the role of surgical procedures for rare esophageal cancers. However, given the rare nature of these diseases, it is still critical that every case be reported in the literature. Our observations and analysis of this group of patients do indicate a positive role for esophagectomies as part of the treatment paradigm for rare esophageal cancers. Because of the limited number of patients, we cannot conclusively determine whether there is a survival benefit for surgical treatment of rare esophageal cancers. However, our experience does suggest that postoperative chemotherapy and radiation did not have a survival benefit, although the number of patients treated was very small.

The most common pathologic features were small cell carcinoma, lymphoma, and undifferentiated carcinoma of the esophagus, with 5 patients in each group (Table 2). Small cell carcinoma of the esophagus was first reported in 1952 and is reported to constitute 0.8% to 2.8% of all

*Table 2. Pathology Results and Surgical Procedure*

| Pathologic Feature | Procedure | Death | Postoperative Survival (Days) |
|---|---|---|---|
| Grade 4 leiomyosarcoma | Ivor Lewis | Yes | 6,852 |
| Grade 4 Undifferentiated carcinoma | Ivor Lewis | Yes | 6,395 |
| Stage IIA small cell undifferentiated | Ivor Lewis | No | 5,565 |
| Stage IIA malignant melanoma | Ivor Lewis | No | 5,520 |
| Stage IA small cell carcinoma | Ivor Lewis | No | 5,509 |
| Grade 3 malignant GIST | Left thoracoabdominal | Yes | 4,198 |
| Grade 1 leiomyosarcoma | Ivor Lewis | Yes | 3,923 |
| Grade 4 small cell carcinoma | Ivor Lewis | Yes | 3,142 |
| High-grade gastrointestinal stromal sarcoma | Transhiatal | No | 2,360 |
| Stage III malignant lymphoma | Ivor Lewis | Yes | 1,423 |
| Grade 3 lymphoma diffuse B-cell type | Ivor Lewis | Yes | 1,166 |
| Stage IIA poorly differentiated neuroendocrine carcinoma | Ivor Lewis | No | 1,100 |
| High-grade sarcomatoid squamous carcinoma | Ivor Lewis | Yes | 1,030 |
| Stage IIA malignant melanoma | McKweon | Yes | 732 |
| High grade primary diffuse large cell lymphoma | McKweon | Yes | 418 |
| Stage III mixed adenoneuroendocrine carcinoma | Ivor Lewis | Yes | 416 |
| Poorly differentiated carcinoma | Ivor Lewis | Yes | 350 |
| High-grade sarcomatoid (spindling) carcinoma | Extended Ivor Lewis with colon interposition | Yes | 248 |
| Grade 3 anaplastic large B-cell lymphoma | Transhiatal | Yes | 226 |
| Grade 4 small cell carcinoma | Ivor Lewis | Yes | 191 |
| Grade 4 sarcoma | Transhiatal | Yes | 185 |
| Invasive undifferentiated carcinoma | Transhiatal | Yes | 132 |
| Stage IB GIST | Ivor Lewis | No | 84 |
| Grade 4 undifferentiated carcinoma | Ivor Lewis | No | LTFU |

GIST = gastrointestinal stromal tumor; LTFU = lost to follow-up.

esophageal cancers [3, 4]. The current literature indicates that approximately 600 cases have been reported [5, 6]. The consensus on treatment, including the role of chemotherapy, radiation, and surgical treatment, remains controversial [6], especially because small cell carcinoma of the lung is largely considered nonsurgical. However, the reports do suggest that surgical resection should be considered in small cell carcinoma of the esophagus, as do our data here [7]. In fact, 3 of the 4 patients with diagnoses of small cell carcinoma have survived more than 8 years after surgical resection. Two of those patients are still alive today, and both are now alive more than 15 years from their resection without recurrence.

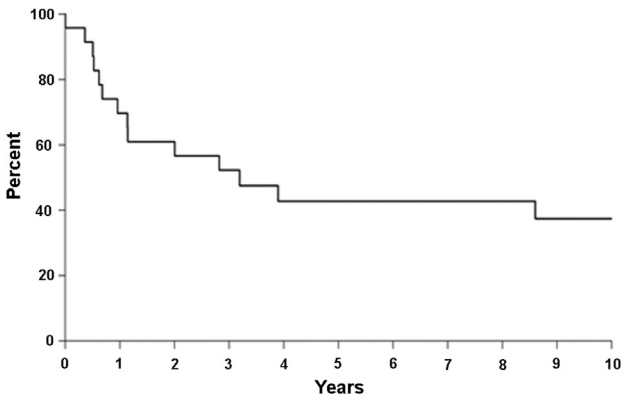


*Fig 1. Overall survival from date of operation to date of death. Six of the patients are currently alive, and 1 patient was lost to follow-up. Median survival is 3.2 years.*

Esophageal lymphoma is extremely rare, accounting for less than 1% of gastrointestinal lymphomas. A review of the literature suggests that fewer than 30 cases have been reported [8, 9]. One risk factor associated with esophageal lymphoma is human immunodeficiency virus. Unfortunately, esophageal lymphoma defines acquired immune deficiency syndrome and is associated with a poor prognosis [10]. Conversely, B-cell lymphoma is a positive prognostic factor [11, 12]. In our experience, 4 patients had resection of an esophageal lymphoma. The average survival was 67 months (range, 18.8 to 118.6 months).

Our review of data also highlighted undifferentiated carcinoma of the esophagus in 4 patients. This rare histologic variant of esophageal cancer is defined as solid sheets of neoplastic cells without significant glandular, squamous, or neuroendocrine features [13–15]. In our data, 1 patient survived 17.5 years, 2 patients died within 1 year after operation, and the last patient was lost to follow-up.

Less common, but equally important, esophageal cancers in our cohort were GIST, melanoma, leiomyosarcoma, sarcomatoid, sarcoma, and neuroendocrine

*Table 3. Kaplan-Meier Estimate*

| Variable | n | Death | Kaplan-Meier Estimates | | | Univariate Cox Models | *P* Value |
|---|---|---|---|---|---|---|---|
| | | | 1-Year Estimate | 5-Year Estimate | 10-Year Estimate | HR (95% CI) | |
| Overall | 24 | 18 | 69.70% (53.25–91.22) | 42.77% (26.47–69.09) | 37.42% (21.67–64.64) | … | … |
| Sex | | | | | | | |
| Female | 7 | 6 | 57.14% (30.08–100.0) | 28.57% (8.86–92.18) | 14.29% (2.33–87.69) | 1.91 (0.69–5.31) | 0.21 |
| Male | 17 | 12 | 75.00% (56.52–99.52) | 48.61% (29.02–81.42) | 48.61% (28.01–81.42) | 1.0 Reference | |
| Previous smoker | | | | | | | |
| No | 12 | 9 | 50.00% (28.40–88.04) | 33.33% (14.98–74.20) | 22.22% (7.17–68.90) | 1.0 Reference | 0.21 |
| Yes | 12 | 9 | 90.91% (75.41–100.0) | 53.03% (29.92–93.99) | 53.03% (29.92–93.99) | 0.53 (0.20–1.44) | |
| Postoperative chemotherapy | | | | | | | |
| No | 14 | 13 | 71.43% (51.29–99.48) | 40.82% (21.26–78.35) | 32.65% (14.88–71.64) | 1.0 Reference | 0.47 |
| Yes | 10 | 5 | 66.67% (42.00–100.0) | 44.44% (21.41–92.27) | 44.44% (19.64–92.27) | 0.68 (0.23–1.95) | |
| Postoperative radiation therapy | | | | | | | |
| No | 19 | 13 | 72.45% (54.52–96.26) | 49.04% (30.34–79.26) | 49.04% (29.47–79.26) | 1.0 Reference | 0.09 |
| Yes | 5 | 5 | 60.00% (29.33–100.0) | 20.00% (3.46–100.00) | | 2.61 (0.86–7.90) | |
| Age (per 10 years) | … | … | … | … | … | 1.30 (0.72–2.33) | 0.39 |

CI = confidence interval; HR = hazard ratio.

tumors. Esophageal GIST represents fewer than 1% of all cases of GIST. A recent publication analyzed a total of 55 pooled esophageal GIST patients and found that they have a significantly worse prognosis than to those with gastric GIST [16]. Of interest, 100% of these tumors have c-Kit mutations, suggesting an important role for imatinib in the treatment paradigm. Esophageal GIST presents with a higher mean mitotic rate and tumor size, making these tumors more aggressive than gastric GIST [16, 17]. In our experience, we have done esophagectomies for 2 patients; 1 patient survived only 84 days, and the other survived more than 11 years.

Primary malignant melanoma of the esophagus (PMME) has fewer than 400 reported cases in the literature [18]. The 5-year survival is reported to be between 2.2% and 37.5% [18–20]. These aggressive tumors present frequently in the lower third of the esophagus, and immunohistochemistry shows positive results for S-100, HMB-45, and melan-A [18]. The general consensus for the treatment of PMME includes esophagectomy with lymph node dissection. In this study, we had 2 patients with PMME, both at stage IIA; 1 patient survived for 2 years and the other for 15 years.

Neuroendocrine tumors of the esophagus more frequently present in the middle third of the esophagus, and they stain positive for synaptophysin, chromogranin A, and CD56 [21, 22]. The general presumption is that neuroendocrine tumors are slow growing; however, high-grade neuroendocrine tumors of the esophagus have a poor prognosis and a 5-year survival of approximately 25% [21, 22].

In conclusion, the need to expand our research efforts in rare esophageal cancer is crucial to the advancement of treatment for this aggressive cancer. Our data suggest that surgical resection can be an integral part of the treatment plan. The 1-year survival after resection is 69%, the 5-year survival is 43%, and the 10-year survival is 37% (Table 3). Although the role for neoadjuvant or postoperative therapy is dependent on the pathologic features, our data here showed no statistical difference in survival for patients who did receive postoperative chemotherapy or radiation therapy (Table 3). In fact, sex and smoking status did not have a significantly impact on survival (Table 3). Our limited data show that leiomyosarcoma (n = 2) had the best survival after surgical resection: of 10.7 years and 18.7 years in 1 patient each. Leiomyosarcomas are malignant smooth muscle tumors that are generally less aggressive then squamous cell carcinoma of the esophagus, thus having better survival, which is consistent with our observations [23, 24]. Unfortunately, 6 patients survived less than 1 year after resection; they included patients with GIST, undifferentiated carcinoma, lymphoma, sarcoma, and sarcomatoid carcinoma [25–27]. The variety of pathologic features in this group of patients surviving less than 1 year can be attributed to low sample size, but it also highlights the aggressive nature of these cancers. It is crucial that we continue to publish our results regarding rare esophageal cancer in the hope that we will be able to improve our surgical decision making and ultimately improve survival from these rare and aggressive cancers.

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