The Impact of Age on Morbidity and Mortality Following Esophagectomy for Esophageal Cancer

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**Background:** In patients with esophageal cancer, treatment decisions often involve a balance between a high-risk procedure and the chance for long-term benefit. The decision can be additionally challenging for elderly patients since some studies have reported an increased incidence of morbidity and mortality in this age group, and data are not clear on the overall benefit of multimodality therapy.

**Methods:** To investigate the management and outcomes associated with esophagectomy in elderly patients with esophageal cancer, we performed a review of the literature as well as an analysis of our own institutional data, with a focus on the impact of age on surgical outcomes. We examined type of surgery, neoadjuvant and adjuvant therapy, postoperative complications, length of hospitalization, and mortality as variables in elderly patients with esophageal cancer.

**Results:** When assessing the impact of age on the success of esophagectomy, several studies have concluded that advanced age itself is not a predictor of outcomes as much as associated comorbidities are. Our own experience suggests that age is not associated with adverse outcomes when controlling for patient comorbidities. This finding is similar to data reported elsewhere.

**Conclusions:** When considering treatment for patients of advanced age, the risks of treatment should be compared with the survival benefits of the therapy prescribed, taking into account additional factors such as poor performance status, existing comorbidities, and residual tumor following neoadjuvant therapy. Many reports, as well as our own experience, have concluded that when adjusted for comorbidities, patient age does not significantly affect outcomes.

**Introduction**

Esophageal cancer continues to increase in incidence worldwide, with squamous cell carcinoma demonstrating a higher incidence than adenocarcinoma. However, the incidence of esophageal squamous cell carcinoma has decreased over the last three decades as esophageal adenocarcinoma has increased. In the United States, esophageal adenocarcinoma is the most common subtype of esophageal cancer, with gastro-esophageal junction tumors comprising the most common location compared with other sites within the
Furthermore, patient age at diagnosis continues to move toward an older onset. In 2013 in the United States, approximately 17,990 new cases of esophageal cancer will be diagnosed and 15,210 related deaths will occur. By sex, the disease will account for about 12,220 deaths in men and 2,990 in women. Esophageal cancer was the seventh leading cause of cancer-related deaths in men in 2012. The overall incidence in men has increased from 7.16 deaths per 100,000 in 1990 to 7.67 per 100,000 in 2007, resulting in a 7.12% increase. By contrast, its incidence in women has been decreasing over the same time period. An increasing number of patients of both sexes are presenting with esophageal cancer at an advanced age, with a peak incidence between 75 and 79 years of age.

The consensus on the ideal treatment modality for esophageal cancer remains controversial for any age group due to conflicting evidence from multiple prospective studies regarding improvement of overall survival (OS). Most centers recommend a multimodality treatment approach of neoadjuvant chemoradiation followed by esophagectomy. The available data suggest that individuals with a complete pathological response achieve significant improvements in OS. When considering treatment for patients of advanced age, the risks of treatment should be compared with the survival benefits of the therapy prescribed. The overall morbidity for esophagectomy is estimated to be between 25% and 50%, and the overall 5-year survival rate with treatment is approximately 25%. The treating team may be reluctant to proceed with therapy, given some initial studies that highlighted an increased incidence of morbidity and mortality in the elderly. The surgeon is often challenged with balancing a high-risk procedure and the marginal chance for long-term cure. The treatment dilemma is confounded by data that are not clear on the overall benefit of multimodality therapy. Several meta-analyses have suggested a benefit from multimodality therapy, but the data do not reach statistical significance in some of these studies. However, many of these data demonstrate heterogeneous patient populations without considering tumor biology or pathological response. In an effort to address the many dilemmas associated with the management of elderly patients with esophageal cancer, we performed a review of the literature as well as an analysis of our own data to investigate outcomes following esophagectomy, highlighting the impact of age on surgical outcomes in this changing paradigm of esophageal cancer.

**Methods**

We performed a comprehensive review of existing data in patients who underwent esophagectomy in order to identify factors that may be associated with adverse outcomes in the aging population. Type of surgery, neoadjuvant and adjuvant therapy, postoperative complications, length of hospitalization, and mortality are among the variables we investigated in elderly patients with esophageal cancer. We also performed an analysis of our own institutional database and investigated outcomes in our elderly patients. A survival analysis was performed utilizing the Kaplan-Meier method, and a multivariate analysis was performed using the Cox proportional hazard regression model.

**Results**

**Surgery and Neoadjuvant Therapy**

In 1993, a multi-institutional retrospective study by Naunheim et al described a 30-day mortality rate of 18% and 68% postoperative morbidity for patients aged 70 years or older who underwent esophagectomy. Only 32% of these patients went through the postoperative course uneventfully. In 1997, Ferguson et al described an operative mortality rate of 13% and an overall morbidity rate of 76% in 269 patients treated surgically for esophageal cancer. Patients aged 70 years or older had a 30-day mortality rate of 25%, which was significantly higher than that seen in other age groups. These data contributed to the concerns about offering esophagectomy to elderly patients with esophageal cancer.

Since the mid 1990s, several studies have sought to identify criteria to select low-risk patients to proceed with multimodality therapy irrespective of age. Specific to the tolerance of neoadjuvant therapy, several studies have evaluated the impact on elderly patients for esophageal cancer. Rice et al identified 74 patients aged 70 years or older who were treated from 1997 to 2002. Of these, 39 were treated with esophagectomy alone (group 1) and 35 were treated with neoadjuvant chemoradiation followed by resection (group 2). Groups 1 and 2 were compared with group 3, which comprised individuals younger than 70 years of age and treated with neoadjuvant chemoradiation followed by esophagectomy. In this retrospective analysis of a prospectively collected database, no difference in postoperative mortality was seen in the three groups. Two differences were noted in postoperative morbidity. First, the incidence in perioperative blood transfusions was higher in group 2 compared with group 3, although no differences were seen in hemoglobin levels. Second, the rate of atrial arrhythmias was higher in groups 1 and 2 than in group 3. OS in patients aged 70 years or more was equivalent to OS in patients younger than 70 years of age.

In addition, Smith et al compared patients receiving Medicare through Surveillance, Epidemiology, and End Results (SEER) data analysis treated...
between 1992 and 2002 with chemoradiation followed by surgery with those treated with single therapeutic modalities. The median age of patients in the study was 72 years, 70% of tumors were in the distal esophagus and gastroesophageal junction, and 73% of the patients had a Charlson comorbidity score of 0. The overall 5-year survival rate was highest for those treated with multimodality treatment, although only 196 of 2,626 patients underwent this type of treatment ($P = .03$). There was no significant difference in mortality between those treated with chemoradiation and surgery compared with those treated with surgery alone. The most common complication was related to an increase in pulmonary complications, including prolonged mechanical ventilation. However, no differences in pulmonary complications were reported between the surgery-only group and the multimodality group (Table 1). Although an underutilized treatment in this analysis, neoadjuvant chemoradiation followed by surgery was well tolerated by patients above 65 years of age and had a better OS rate when compared with other single-modality therapies. This study did note a trend toward an increasing use of multimodality therapy as the study progressed. Furthermore, those treated with a surgical approach had a lower Charlson comorbidity score compared with those given nonsurgical therapy.

Numerous reports have evaluated the impact of complex surgery in the elderly, and many researchers have concluded that, when adjusted for comorbidities, patient age does not significantly affect outcomes.$^{30,31}$ The implication from existing data is that a select group of elderly patients can tolerate a major operation. Individual studies have highlighted that selected septuagenarians and octogenarians tolerate esophagectomy at a rate similar to those who are younger than 70 years of age. Conversely, when risk factors are prospectively assessed, age is often cited as a contributor to increased perioperative mortality.$^{32}$

When assessing the impact of age and esophagectomy, most studies have concluded that advanced age itself is not a predictor of outcomes as much as the associated comorbidities are. Fang et al$^{33}$ evaluated patients aged 70 years or older undergoing a three-field esophagectomy. This study compared 79 patients aged 70 years and above with 362 patients below the age of 70 years. The overall mortality rate was slightly higher in the elderly group, although this was not statistically significant. While the morbidity rate was equivalent, a higher rate of multiorgan dysfunction and postoperative infection occurred in the elderly patients.

Several studies have highlighted similar patterns of data as demonstrated in the Fang et al$^{33}$ study (Table 2).$^{26,31,34-40}$ There does appear to be an increase in overall mortality and a decrease in OS with advancing age.$^{39}$ However, when adjusted for comorbidities, the outcomes are similar across age groups.$^{40}$

**Institutional Experience**

We investigated our own comprehensive esophageal cancer database, which consists of 685 patients, to determine not only the correlation between age and outcomes related to esophagectomy, but also the impact of neoadjuvant therapy on elderly patients ($\geq 70$ years). We demonstrated an OS benefit in patients younger than 70 years ($n = 456$) compared with their counterparts older than 70 years ($n = 229$; $P = .04$). However, when investigating the impact on disease-free survival, significance was not main-

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**Table 1. — Postoperative Outcomes in Patients Aged > 65 Yrs Treated With Surgery Alone vs Preoperative CRT Plus Surgery**

<table>
<thead>
<tr>
<th>Postoperative Outcome</th>
<th>Surgery Alone, % (n)</th>
<th>CRT + Surgery, % (n)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death within 60 d of surgery$^a$</td>
<td>13 (105)</td>
<td>0 (0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Postoperative Complications During Surgical Admission$^b$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia/pneumonitis</td>
<td>15 (74)</td>
<td>12 (17)</td>
<td>.34</td>
</tr>
<tr>
<td>ARDS/mechanical ventilation</td>
<td>30 (148)</td>
<td>25 (36)</td>
<td>.25</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>6 (30)</td>
<td>6 (9)</td>
<td>.93</td>
</tr>
<tr>
<td>Sepsis</td>
<td>8 (40)</td>
<td>8 (11)</td>
<td>.86</td>
</tr>
<tr>
<td>$\geq 1$ of the above complications</td>
<td>42 (207)</td>
<td>35 (50)</td>
<td>.12</td>
</tr>
<tr>
<td>Median length of stay for surgical admission (interquartile range)$^c$</td>
<td>15 (10-26)</td>
<td>12 (9-18)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Readmission within 1 yr for pulmonary complication$^d,e$</td>
<td>2 (17)</td>
<td>2 (4)</td>
<td>.93</td>
</tr>
</tbody>
</table>

$^a$ Total $n = 792$ (surgery alone) and 196 (CRT + surgery).

$^b$ Total $n = 488$ (surgery alone) and 142 (CRT + surgery), based on patients with known dates for surgery.

$^c$ Pneumonia, radiation pneumonitis, ARDS, or mechanical ventilation.

$^d$ ARDS = acute respiratory distress syndrome, CRT = chemoradiotherapy.

tained ($P = .28$; Figs 1 and 2). We then performed a multivariate analysis utilizing the Cox proportional hazard regression model to investigate the correlation between survival and age, controlling for age-related comorbidities such as diabetes, hypertension, chronic obstructive pulmonary disease (COPD), coronary artery disease, cerebrovascular accident, congestive heart failure, peripheral vascular disease, smoking, and neoadjuvant therapy. We confirmed that the only significant predictor of OS and disease-free survival on multivariate analysis was neoadjuvant therapy, with hazard ratios (HRs) of 2.43 (95% confidence interval [CI], 1.04-5.7; $P = .041$) and 2.16 (95% CI, 1.1-4.2; $P = .02$), respectively. In addition, COPD was significant only in OS, with an HR of 4.4 (95% CI, 1.5-12.3; $P = .005$). Age was not associated with adverse outcomes when controlling for patient comorbidities ($P = .66$). This finding is similar to data reported by Fogh et al$^{41}$ in their series of 260 patients receiving neoadjuvant chemoradiotherapy followed by esophagectomy.

Table 2. — Studies Showing That Advanced Age Is Not a Predictor of Esophagectomy Outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>Age (yrs)</th>
<th>No. of Patients</th>
<th>Morbidity (%)</th>
<th>30-day Mortality Rate (%)</th>
<th>In-Hospital Mortality Rate (%)</th>
<th>Overall Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellis$^{34}$</td>
<td>≥ 70</td>
<td>147</td>
<td>37.6</td>
<td>4.5</td>
<td>5.3</td>
<td>24.1</td>
</tr>
<tr>
<td></td>
<td>&lt; 70</td>
<td>358</td>
<td>32.3</td>
<td>1.25</td>
<td>2.4</td>
<td>22.4</td>
</tr>
<tr>
<td>Alexiou$^{35}$</td>
<td>≥ 70–86</td>
<td>186</td>
<td>34.4</td>
<td>–</td>
<td>6.4</td>
<td>21.2</td>
</tr>
<tr>
<td></td>
<td>&lt; 70</td>
<td>337</td>
<td>24.7</td>
<td>–</td>
<td>4.7</td>
<td>25.1</td>
</tr>
<tr>
<td>Poon$^{36}$</td>
<td>≥ 70</td>
<td>167</td>
<td>&gt; 39.5</td>
<td>7.2</td>
<td>18.0</td>
<td>26.0</td>
</tr>
<tr>
<td></td>
<td>&lt; 70</td>
<td>570</td>
<td>&gt; 28.1</td>
<td>3.0</td>
<td>14.4</td>
<td>35.0</td>
</tr>
<tr>
<td>Jougon$^{37}$</td>
<td>≥ 70</td>
<td>89</td>
<td>24.7</td>
<td>–</td>
<td>7.5</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>&lt; 70</td>
<td>451</td>
<td>26.8</td>
<td>–</td>
<td>5.3</td>
<td>20.7</td>
</tr>
<tr>
<td>Thomas$^{38}$</td>
<td>≥ 70</td>
<td>56</td>
<td>50.0</td>
<td>8.9</td>
<td>10.7</td>
<td>17.0</td>
</tr>
<tr>
<td></td>
<td>&lt; 70</td>
<td>330</td>
<td>57.3</td>
<td>7.9</td>
<td>11.2</td>
<td>18.9</td>
</tr>
<tr>
<td>Nauheim$^{36}$</td>
<td>≥ 70</td>
<td>38</td>
<td>68</td>
<td>–</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Fang$^{39}$</td>
<td>≥ 70</td>
<td>79</td>
<td>65.8</td>
<td>3.3</td>
<td>8.9</td>
<td>40.9</td>
</tr>
<tr>
<td></td>
<td>&lt; 70</td>
<td>362</td>
<td>61.6</td>
<td>0.8</td>
<td>3.8</td>
<td>48.1</td>
</tr>
<tr>
<td>Mortiz$^{37}$</td>
<td>&gt; 80</td>
<td>16</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>70–79</td>
<td>158</td>
<td>42</td>
<td>8</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>&lt; 70</td>
<td>494</td>
<td>32</td>
<td>7</td>
<td>3</td>
<td>39</td>
</tr>
<tr>
<td>Moskovitz$^{38}$</td>
<td>&gt; 80</td>
<td>31</td>
<td>&gt; 32</td>
<td>–</td>
<td>6</td>
<td>16.8 mos</td>
</tr>
<tr>
<td></td>
<td>70–79</td>
<td>207</td>
<td>&gt; 22</td>
<td>–</td>
<td>15</td>
<td>29.1 mos</td>
</tr>
<tr>
<td>Ruol$^{40}$</td>
<td>≥ 70</td>
<td>165</td>
<td>49.1</td>
<td>1.9</td>
<td>1.9</td>
<td>35.4</td>
</tr>
<tr>
<td></td>
<td>&lt; 70</td>
<td>599</td>
<td>48.6</td>
<td>1.9</td>
<td>2.7</td>
<td>33.6</td>
</tr>
</tbody>
</table>

Fig 1. — Probability of overall survival in patients aged < 70 and ≥ 70 years of age. Data taken from the Moffitt Cancer Center’s esophageal cancer database.

Fig 2. — Disease-free survival in patients < 70 and ≥ 70 years of age. Data taken from the Moffitt Cancer Center’s esophageal cancer database.
They demonstrated no difference in survival in patients aged 70 years or older compared with those younger than 70 years ($P = .2$).

**Discussion**

**Predictive Modeling**

With mounting evidence that age alone should not prevent a patient from undergoing a complex surgery, attention has been focused on predictive models to identify those who would benefit from surgery. Copeland et al. designed the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) algorithm to predict the risk of mortality for surgical procedures. This initial algorithm often overpredicted the risk of mortality for a given procedure, which led to the development of a second-generation algorithm, the POSSUM, Portsmouth modification (P-POSSUM). This updated model used the same operative and physiologic predictors but incorporated an upgraded regression equation. The P-POSSUM algorithm has demonstrated improved predictability for complex surgical procedures and can be used as a reliable tool to predict mortality. This P-POSSUM algorithm is designed primarily to assess risk of perioperative mortality rather than for complications or morbidity.

Since the development of the P-POSSUM algorithm, several specialty-specific models have been developed, with the oesophagogastric model (O-POSSUM) designed for gastric and esophageal surgery. Tekkis et al. developed the O-POSSUM algorithm to focus primarily on these surgical outcomes. The initial study of 538 patients undergoing either a gastric or an esophageal resection highlighted that multiple risk factors contributed to mortality. The urgency of surgery, the preoperative stage, the type of surgery, and the preoperative POSSUM score were factors used to calculate risk. The initial evaluation demonstrates an age-associated risk for mortality based on these metrics (Fig 3).

Bosch et al. recently compared five risk-prediction models for esophagectomy-related morbidity and mortality. The P-POSSUM, the O-POSSUM modification, the Charlson comorbidity index with the age-adjusted Charlson score version, and the standard American Society of Anesthesiologists (ASA) classification systems were used to determine the best predictive model for expected mortality following an esophagectomy. This study concluded that P-POSSUM and O-POSSUM were both beneficial tools. While

![Figure 3. Comparison of observed in-hospital operative mortality (with 95% confidence intervals) across four age groups and the results predicted by the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity, Portsmouth modification (P-POSSUM), the single-level (SL) scoring system specific for upper gastrointestinal surgery (O-POSSUM), and the multilevel (ML) O-POSSUM scoring system. From Tekkis PP, McCulloch P, Poloniecki JD, et al. Risk-adjusted prediction of operative mortality in oesophagogastric surgery with O-POSSUM. Br J Surg. 2004;91(3):288-295. Copyright © 2004 British Journal of Surgery Society Ltd. Published by John Wiley & Sons, Ltd.](image-url)
the P-POSSUM trended toward an overprediction of mortality, overall it was the most accurate tool to assess perioperative risk within risk-stratified cohorts. Moreover, the P-POSSUM was also the most useful in a retrospective assessment, whereas the O-POSSUM was more accurate in predicting an individual’s prospective perioperative risk (Table 3).

Using a less complex approach, Dhungel et al47 used the National Surgical Quality Improvement Program database of the American College of Surgeons to assess perioperative risk factors to predict postoperative complications. These values were subdivided based on each specific complication. The highest risks for morbidity and mortality were related to diabetes mellitus, advanced age, preoperative weight loss, and pulmonary disease. An exact algorithm was not developed, but specific perioperative risk factors were identified for age such as respiratory complications (P = .01), deep venous thrombosis (P = .01), and death (P = .01). However, wound, cardiac, reoperations, and sepsis were not risk factors (P = not significant) among any groups.

Ra et al48 used a conglomeration of metrics to calculate risk. They utilized a combination of the Charlson comorbidity index, age, and hospital volume to predict postoperative mortality. The data were taken from the SEER database from 1997 to 2003. There was an increase in mortality that paralleled an increased age. The mortality rates were 10% for those between the ages of 65 and 69 years and 18% for those above the age of 80 years. However, when compared with the predictive risk model developed in this study, those with a risk score of 0 had a 4% mortality rate compared with a mortality rate higher than 20% for those with a score of 4 or above. Therefore, the comorbidities were more important factors than specific age.

Zingg et al49 compared four distinct risk-assessment models for esophagectomy cohorts in Australia and Switzerland. The models included were from Philadelphia, Munich, Rotterdam, and the ASA. None of the risk-assessment models accurately predicted postoperative mortality for the combined cohort, although individual country subgroups were more accurate with certain models. This study suggested that hospital systems and surgeon-specific techniques might be significant contributors to outcomes, along with patient-specific comorbidities.

Conclusions

Elderly patients with esophageal cancer represent a diverse cohort in whom health care professionals should strongly consider esophageal resection. Multimodality therapy for esophageal cancer can be offered to the elderly patient without an increase in adverse outcomes following therapy. In addition, when corrected for comorbidities, elderly patients have morbidities and mortalities following surgery that are similar to those of their younger counterparts. The focus of the practicing physician is to identify and use a predictive model to determine which individuals are at a high risk for perioperative complications and might not benefit from surgical therapy. The evidence suggests there is a risk-benefit balance where proceeding with surgery may not offer a survival benefit, specifically in elderly patients with a poor performance status, several comorbidities, and residual tumor following neoadjuvant therapy. The available algorithms may aid in the recommendation to either proceed with surgery or avoid resection.

References


