Influence of Patients' Age in the Utilization of Esophagectomy for Esophageal Adenocarcinoma

Francisco Schlottmann, MD, MPH,^{1,2} Paula D. Strassle, MSPH,^{1,3}
Daniela Molena, MD,⁴ and Marco G. Patti, MD^{1,5}

Abstract

Background: The indication of surgical resection in esophageal cancer is often conditioned by patient's age. We aimed to assess the trends in utilization of surgical treatment for esophageal adenocarcinoma (EAC) in the United States, stratified by age groups.

Methods: We performed a retrospective analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results program registry for the period 2004–2014. Adult patients (aged ≥ 18 years) diagnosed with EAC were eligible for inclusion. The yearly incidence of esophagectomy, stratified by age groups (18–49, 50–70, and >70 years old), was calculated using Poisson regression. Weighted log-binomial regression was used to compare the proportion of patients undergoing esophagectomy, within each age group. Inverse probability of treatment weights were used to account for potential confounders.

Results: A total of 21,301 patients were included. During the study period, the rate of esophagectomy decreased from 34.1% to 28.2% ($P=.40$) in patients between 18 and 49 years old, from 38.6% to 33.3% ($P=.06$) in patients between 50 and 70 years old, and from 21.4% to 16.9% ($P=.04$) in patients older than 70 years. After accounting for patient and cancer characteristics, patients older than 70 years were 50% less likely to undergo esophagectomy compared with both patients between 18 and 49 years old (risk ratio [RR] 0.51, 95% confidence interval [CI] 0.45–0.57, $P<.0001$) and patients between 50 and 70 years old (RR 0.53, 95% CI 0.50–0.56, $P<.0001$).

Conclusion: Surgical resection is scarcely used in patients older than 70 years in the United States. Further investigation of surgical outcomes in elderly patients is warranted to determine if surgical treatment is underutilized in a large proportion of EAC patients.

Keywords: esophageal adenocarcinoma, esophagectomy, elderly

Introduction

ESOPHAGEAL CANCER IS the eighth most common cancer worldwide, with an estimated 456,000 new cases and 400,000 deaths in 2012.¹ Specifically, the incidence of esophageal adenocarcinoma (EAC) has increased more than six-fold in Western countries over the past 40 years.² This increase has been attributed to the rising prevalence of obesity and gastroesophageal reflux disease.

Esophageal cancer rarely affects young patients and is most frequently diagnosed among people aged 65–74 years, with a

median age at diagnosis of 67 years.³ The rising incidence of EAC and the progressing aging of the population will likely lead to an increase in the number of elderly patients with EAC.⁴ Although esophagectomy remains the cornerstone for the treatment of EAC, the procedure is associated with significant morbidity and mortality.^{5,6} For this reason, the indication for surgical resection is often influenced by patient's age.

We hypothesized that the utilization of surgical treatment is influenced substantially by patient's age. Therefore, we aimed to assess the trends in utilization of surgical treatment for EAC in the United States, stratified by age groups.

¹Department of Surgery, University of North Carolina School of Medicine, Chapel Hill, North Carolina.

²Department of Surgery, Hospital Alemán of Buenos Aires, University of Buenos Aires, Buenos Aires, Argentina.

³Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

⁴Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York.

⁵Department of Medicine, University of North Carolina, Chapel Hill, North Carolina.

Methods

Study design and population

Using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program registry, adults who were ≥ 18 years old with diagnosis of EAC between 2004 and 2014 were eligible for inclusion. The SEER program prospectively collects de-identified information on individuals diagnosed with cancer from 18 registries across the United States and covers roughly 30% of the population. Esophagectomy was identified using the following SEER surgery codes: 30, 40, 50–55, and 80.

Statistical analyses

Patient demographics and cancer characteristics, stratified by age groups (categorized as 18–49, 50–70, and >70 years old), were described using frequency tables and bivariate analyses. The yearly incidence of EAC, stratified by patient's age, and 95% confidence interval (CI) were calculated using Poisson regression. Significant changes in trends over time were assessed using a likelihood ratio test.

Unadjusted and weighted log-binomial regression was used to estimate the utilization of surgical treatment within each age group. Inverse probability of treatment weights (IPTW) were used to account for potential confounding by patient and cancer characteristics. Generalized logistic regression was used to estimate the probability of each patient being diagnosed at the age they did, given their year of diagnosis, sex, race/ethnicity, region, whether it was the patient's first cancer diagnosis, tumor grade, derived American Joint Committee on Cancer (AJCC, sixth edition), *T* value, derived AJCC *N* value, derived AJCC *M* value, radiation treatment, and chemotherapy status. The weights were then standardized by the marginal probability of being in each age group. These weighting methods are preferable to traditional adjustment methods because they effectively equalize the distribution of the above patient and cancer characteristics across each age group, removing any confounding, and they allow for the marginal (i.e., overall) cumulative incidence of esophagectomy to be estimated, as opposed to the conditional (i.e., adjusted) cumulative incidence.

To account for the missing data in tumor grade ($n=4052$, 19.0%), derived AJCC *T* value ($n=4929$, 23.1%), derived AJCC *N* value ($n=2921$, 13.7%), and derived AJCC *M* value ($n=1415$, 6.6%), inverse probability of missingness weights (IPMW) were used. The probability of being a complete case (i.e., no missing data) was estimated using multivariable logistic regression, adjusting for year of diagnosis, sex, age category, race/ethnicity, region, whether it was the patient's first cancer diagnosis, tumor grade, radiation treatment, and chemotherapy status. IPMW for each patient were stabilized using the overall probability of being a complete case, stratified by age groups.

The IPTW and IPMW for each patient were then multiplied together and truncated at the 5th and 95th percentiles to create the final overall weight for each patient. Robust sandwich estimators were used to estimate the 95% CIs to account for the weights.

A *P* value $< .05$ was considered significant for all the statistical methods. All statistical analyses were performed using SAS 9.4 (SAS, Inc., Cary, NC).

Results

Overall, 21,301 patients with EAC were included in the analysis: 1560 (7.3%) patients were between 18 and 49 years old, 11,384 (53.4%) were between 50 and 70 years old, and 8357 (39.2%) were older than 70 years. Patient and tumor characteristics, stratified by age groups, are described in Table 1.

Between 2004 and 2014, the incidence of esophagectomy decreased from 34.1% to 28.2% ($P = .40$) in patients between

TABLE 1. DISTRIBUTION OF PATIENT AND TUMOR CHARACTERISTICS, STRATIFIED BY AGE GROUPS

	18–49 Years old	50–70 Years old	>70 Years old
	1560 (7.3%)	11,384 (53.4%)	8357 (39.2%)
Sex, <i>n</i> (%)			
Female	190 (12.2)	1254 (11.0)	1580 (18.9)
Male	1370 (87.8)	10,130 (89.0)	6777 (81.1)
Race/ethnicity, <i>n</i> (%)			
White	1271 (81.5)	10,004 (88.2)	7515 (90.2)
Black	48 (3.1)	355 (3.1)	163 (2.0)
Asian/Pacific Islander	54 (3.5)	244 (2.2)	191 (2.3)
Hispanic	187 (12.0)	746 (6.6)	462 (5.6)
Region, <i>n</i> (%)			
Northeast	266 (17.1)	1953 (17.2)	1600 (19.2)
Midwest	192 (12.3)	1392 (12.2)	1033 (12.4)
South	421 (27.0)	2745 (24.0)	1403 (16.8)
West	681 (43.7)	5304 (46.6)	4321 (51.7)
Tumor grade, <i>n</i> (%)			
Grade 1	63 (5.0)	538 (5.8)	427 (6.4)
Grade 2	540 (42.5)	3882 (41.8)	2756 (41.3)
Grade 3	668 (52.6)	4876 (52.5)	3499 (52.4)
Missing	289	2088	1675
AJCC <i>T</i> value, <i>n</i> (%)			
T0/Tis	18 (1.5)	96 (1.1)	92 (1.5)
T1	355 (29.4)	3021 (33.4)	2424 (39.6)
T2	138 (11.4)	1104 (12.2)	793 (12.9)
T3	472 (39.0)	3572 (39.5)	2056 (33.6)
T4	226 (18.7)	1244 (13.8)	761 (12.4)
Missing	351	2347	2231
AJCC <i>N</i> value, <i>n</i> (%)			
N0	502 (36.8)	4527 (44.9)	3878 (56.0)
N1	863 (63.2)	5562 (55.1)	3048 (44.0)
Missing	195	1295	1431
AJCC <i>M</i> value, <i>n</i> (%)			
M0	724 (48.6)	6268 (57.8)	5026 (66.6)
M1	765 (51.4)	4584 (42.2)	2519 (33.4)
Missing	71	532	812
First cancer diagnosis, <i>n</i> (%)			
Yes	1484 (95.1)	9995 (87.8)	5987 (71.6)
No	76 (4.9)	1389 (12.2)	2370 (28.4)
Radiation therapy, <i>n</i> (%)			
Yes	840 (54.7)	6296 (55.9)	3926 (71.6)
No/unknown	695 (45.3)	4975 (44.1)	2370 (28.4)
Chemotherapy, <i>n</i> (%)			
Yes	1154 (74.0)	7813 (68.6)	3903 (46.7)
No/unknown	406 (26.0)	3571 (31.4)	4454 (53.3)

AJCC, American Joint Committee on Cancer.

18 and 49 years old, from 38.6% to 33.3% ($P=.06$) in patients between 50 and 70 years old, and from 21.4% to 16.9% ($P=.04$) in patients older than 70 years (Fig. 1).

After accounting for patient and tumor characteristics, patients older than 70 years were almost 50% less likely to undergo esophagectomy compared with both patients between 18 and 49 years old (risk ratio [RR] 0.51, 95% CI 0.45–0.57, $P<.0001$) and patients between 50 and 70 years old (RR 0.53, 95% CI 0.50–0.56, $P<.0001$) (Table 2).

No significant difference in utilization of surgical treatment was seen in patients between 50 and 70 years old when compared with those between 18 and 49 years old (RR 0.95, 95% CI 0.86–1.05, $P=.34$) (Table 2).

Discussion

We aimed to characterize the trends in utilization of surgical resection for EAC across patient's age. We found a decrease in rates of esophagectomy in all age groups between 2004 and 2014. However, elderly patients were significantly less likely to undergo esophagectomy than their younger counterparts, even after accounting for patient demographics and cancer characteristics.

Esophagectomy is a technically challenging procedure, requiring advanced surgical skills and adequate postoperative care. Even in high-volume centers, the overall complication rate is around 60%.⁷ Therefore, there is great emphasis on identifying appropriate candidates for resection to minimize perioperative morbidity and mortality. Interestingly, whether a patient's age has a detrimental effect on surgical outcomes remains controversial. Theoretically, age-related changes can lead to a decreased physiological reserve, which could potentially adversely affect elderly patients during a severe physical stress, such as an esophagectomy. However, previ-

ous reports have shown that elderly patients have similar morbidity and mortality rates than younger patients.^{8–10} For instance, Ruol et al.⁹ compared the postoperative outcomes of 159 patients ≥ 70 years old and 580 patients <70 years old at a single institution and found that the rates of overall morbidity (49.1% versus 48.6%), in-hospital mortality (1.9% versus 2.7%), and 30-day mortality (1.9% versus 1.9%) were similar in both the groups. Similarly, Paulus et al.¹⁰ reported that postoperative morbidity, mortality, and length of stay in octogenarians were comparable to younger patients.

Despite these results, few elderly patients with esophageal cancer seem to undergo surgery. Molena et al.¹¹ analyzed a cohort of 5072 esophageal cancer patients older than 65 years and found that 34.74% of the patients received no treatment of any kind, and among those who received treatment, the vast majority received definitive chemoradiation. Paulson et al.¹² reported that the odds of surgical intervention in patients aged 75–79 years were half those of patients aged 65–74 years. Consistent with these results, we found that patients older than 70 years were 50% less likely to undergo esophagectomy compared with both patients between 18 and 49 years old and patients between 50 and 70 years old. Our data support that, even with great advances in surgical technique, anesthesia, and postoperative care, age continues to be determinant when deciding the treatment modality in elderly patients with esophageal cancer. It is worth mentioning, however, that a lower rate of esophagectomy in patients older than 70 years may also be related to patient's choice and denial to undergo surgical treatment.

Interestingly, we found an overall decrease in the utilization of surgical resection across all age groups between 2004 and 2014 (although it was only statistically significant in patients older than 70 years). This could be explained, in part, by the development of new endoscopic treatment modalities

FIG. 1. Utilization of esophagectomy for esophageal adenocarcinoma during the period 2004–2014, stratified by age groups.

TABLE 2. CRUDE AND STANDARDIZED INCIDENCE OF ESOPHAGECTOMY FOR ESOPHAGEAL ADENOCARCINOMA, STRATIFIED BY AGE GROUPS

	<i>Crude</i>			<i>Standardized^a</i>		
	<i>ESO %</i>	<i>RR (95% CI)^b</i>	<i>P</i>	<i>ESO %</i>	<i>RR (95% CI)^b</i>	<i>P</i>
18–49 years old	32.5	ref	—	50.8	Ref	—
50–70 years old	35.1	1.08 (1.00–1.17)	.05	48.4	0.95 (0.86–1.05)	.34
>70 years old	16.6	0.51 (0.47–0.56)	<.0001	25.7	0.51 (0.45–0.57)	<.0001

^aStabilized inverse probability of treatment weights (IPTW) were created adjusting for year of diagnosis, patient sex, race/ethnicity, region, cancer grade, first cancer diagnosis, derived American Joint Committee on Cancer (AJCC) *T* value, derived AJCC *N* value, derived AJCC *M* value, radiation therapy, and chemotherapy status.

^bCI's were estimated using robust sandwich estimators to account for the weights.

p-values < 0.05 are denoted in bold.

ESO, esophagectomy; RR, risk ratio; CI, confidence interval.

and good outcomes in early-stage esophageal cancer.^{13–15} Taylor et al.¹⁶ analyzed a cohort of esophageal cancer patients from the National Cancer Database and found that the use of local therapies doubled from 13.6% to 27.4% for early-stage esophageal cancer between 2004 and 2013. In line with our results, they also reported that more than half of the patients received exclusively nonsurgical therapies or did not undergo treatment, and age was significantly associated with the use of esophagectomy.¹⁶ In addition, health disparities may also play a role in the underutilization of esophageal cancer surgery. For instance, a previous study showed that blacks and Hispanics were less likely to undergo esophagectomy and had a higher risk of mortality compared with white patients.¹⁷ Similarly, Greenstein et al.¹⁸ included 1522 patients with esophageal cancer in their study and found that black patients were more likely to be diagnosed at a more advanced stage and were less likely to undergo surgery than white patients were. Lineback et al.¹⁹ found that esophageal cancer patients with low socioeconomic status were offered operative treatment at significantly lower rates (44.7% versus 76.3%), had a decreased rate of second opinions (23.8% versus 65.8%), and were more likely to lose their jobs (33.3% versus 2.6%) than their high socioeconomic status counterparts. Communication difficulties, lack of understanding of treatment, and financial difficulties were reported more frequently in the lower socioeconomic groups.

This study has several limitations. The SEER program registry is a large administrative data set with the potential for coding errors and differences in coding practices across hospitals. Another significant limitation is that we could not determine the reasons why patients were or were not offered surgical resection. However, we attempted to minimize this bias by accounting for cancer characteristics in our weighted models. In addition, we were unable to define the performance status or frailty of our patients, which may have influenced the denial of surgery in a large proportion of elderly patients. For instance, age could be an important surrogate of patients' comorbidities.

Despite these limitations, we demonstrated that there has been a decrease in the use of surgery in elderly patients, and these patients were significantly less likely to undergo esophagectomy compared with their younger counterparts. Referral of esophageal cancer patients to specialized centers may result in an increase of surgical resection rates.²⁰

In conclusion, surgical resection is scarcely used in patients older than 70 years in the United States, and they are signifi-

cantly less likely to have surgery compared with their younger counterparts. Further investigation of surgical outcomes in elderly patients is needed to determine if surgical treatment is underutilized in a large proportion of EAC patients.

Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Francisco Schlottmann, MD, MPH
Department of Surgery
University of North Carolina School of Medicine
101 Manning Drive, CB 7081
Chapel Hill, NC 27599-7081

E-mail: fschlottmann@hotmail.com