Original Article

Association of Age and Survival in Patients With Gastroesophageal Cancer Undergoing Surgery With or Without Preoperative Therapy

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BACKGROUND: Meticulous selection of patients for esophageal cancer surgery is critical, because major surgical intervention can cause considerable consequences. For this study, the authors explored their institution's large surgical experience to examine the impact of age on long-term patient survival and surgical complications. **METHOD:** Six hundred consecutive patients with esophageal cancer who underwent surgery (409 patients received preoperative therapy, and 191 patients underwent surgery first) were analyzed. All demographic information (including American Society of Anesthesiology risk scores) and therapy-related information was collected retrospectively. Multiple statistical methods were used to assess survival rates and surgical complications and their correlation with patient age. Twenty-one patients (30-day mortality) first were excluded (n = 600) and then were included (n = 621) in the analysis. **RESULTS:** By using the median age (≤60 years) as the cutoff point and creating 2 subgroups (ages 61 years to 70 years and aged >70 years) in patients older than the median age, univariate analysis demonstrated a higher risk of death with increasing age ($P = .019$). In multivariate analysis, increasing age was an independent prognosticator of poor overall survival ($P = .041$). The inclusion of 30-day mortality did not alter the results. Surgical complications were statistically significantly higher in older patients compared with younger patients in the following categories: aspiration pneumonia, adult respiratory distress syndrome, cardiovascular, neurologic, and miscellaneous complications. **CONCLUSIONS:** The data in this study demonstrated that patients aged ≤60 years who underwent surgery for esophageal cancer achieved the best overall survival and experienced fewer surgical complications than patients aged >70 years. Age was identified as an important variable in the selection of patients for esophageal cancer surgery. **Cancer 2009;115:4450–8. © 2009 American Cancer Society.**

KEY WORDS: esophageal surgery, surgical mortality, age and outcome, preoperative therapy, patient selection.

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The incidence of esophageal or gastroesophageal adenocarcinoma has increased considerably in the West over the past 25 years. The most recent analysis suggests that esophageal adenocarcinoma is a disease that will become quite common in North America in the next 20 years.[1] In 2008, an estimated 16,500 new cases of esophageal cancer will be diagnosed, and they will be responsible for the deaths of approximately 14,000 patients.[2] For patients who have localized adenocarcinoma of the esophagus or the gastroesophageal junction, surgery either as primary therapy or after preoperative therapy frequently is considered as definitive local therapy. However, all therapies that are used to control esophageal cancer are associated with considerable morbidity and mortality.[3,4] Internullo et al[5] reported on 180 patients with esophageal cancer patients aged >75 years who had a 5-year survival rate of 36% and a postoperative morbidity rate of 52%. However, those authors did not compare their results with results from patients aged <75 years. A recent Japanese study by Morita et al[6] examined surgical morbidity and mortality in patients aged ≥80 years, ages 70 years to 79 years, and aged ≤69 years. Although Japanese patients are different from western patients in terms of weight and comorbidities, older Japanese patients in that study had higher morbidity and mortality (but not necessarily patients aged ≥80 years, although only there were only 16 patients in that category). Rice et al[7] from our group reported a previous experience that compared 74 patients aged >70 years with 165 patients aged <70 years and suggested that elderly patients did not suffer excessive postoperative complications. Limited survival comparisons (of subgroups only) were reported. We believe that our previous report and other reports have not completely resolved the question of the impact of age on outcome or complications. Currently, there is an increased awareness of the distinctive biology of cancer in patients of different ages with the immediate consequence of a need to address the distinctive impact of age on this disease and its management through translational and clinical research.[8]

In this report, we present 1 of the largest single-institution experiences to date, 600 consecutive patients with esophageal cancer who underwent surgery and we examine the impact of age on long-term survival and surgical complications. Our focus was entirely on those patients who underwent surgery, and patients who did not undergo surgery were not considered. In addition, the details regarding specific chemoradiation protocols and specific cytotoxic agents are not presented, mainly because our emphasis was on long-term survival and not on complications before surgery.

MATERIALS AND METHODS

Patient Identification and Selection

From the database of the Department of Thoracic and Cardiovascular Surgery, we identified 600 consecutive patients who had gastroesophageal junction or esophageal carcinoma (Siewert type I and type II[9]) who underwent surgical resection with curative intent between 1998 and 2007 at The University of Texas M. D. Anderson Cancer Center. All eligible patients were aged ≥18 years and had biopsy-proven esophageal carcinoma. All patients had to be medically fit for surgery and had to have localized carcinoma. Disease stage was determined based on the American Joint Committee on Cancer TNM staging, sixth edition.[10] This analysis was approved by the Institutional Review Board.

Data Collection

Only medically fit patients who had resectable cancers (stage I to IVA) and who underwent surgery were included in this analysis. We extracted data on age, sex, and preoperative American Society of Anesthesiology (ASA) risk score (available at: http://en.wikipedia.org/wiki/ASA_score accessed September 2008). In addition, we collected tumor characteristics at baseline to include the location of the primary (upper, middle or lower third of the esophagus), clinical stage (tumor classification [T], lymph node status [N], and metastasis status [M]), and histology (adenocarcinoma vs squamous carcinoma). Pretreatment staging was determined based on history, complete physical examinations, computed tomography (CT) scans of the chest and abdomen (and pelvis when indicated), and endoscopic ultrasound findings. Positron emission tomography-CT results were collected when available. We also collected pathologic stage and surgical complications (pulmonary, cardiovascular, neurologic, infectious, and various others). We gathered information on local, regional, and distant recurrences and on survival for all patients. To examine the impact of age on the long-term survival of our patients, we analyzed survival in 2 subgroups: The first group was derived by excluding any patient who died within 30 days of surgery (surgical mortality; n = 600), and the second group (n = 621) included patients who died either in the hospital after surgery or within 30 days of surgery as a result of surgical intervention.

Therapy

Depending on the clinical stage (for example, stage I cancer) or other circumstances (active bleeding at presentation or patient's preference), some patients underwent surgery as primary therapy. However, most patients received preoperative therapy before they underwent surgery. Preoperative chemotherapy consisted of most often of 2 drugs from 1 of the 4 classes of cytotoxics commonly used to treat this group of patients (fluoropyrimidine, platinum compound, taxane, and camptothecin).[11] Details of specific protocols and cytotoxic agents are not presented. Radiation therapy most often was delivered at 1.8 grays per fraction with 6-megavolt to 18-megavolt photons.

Statistical Analysis

First, chi-square and Fischer exact tests were used to examine whether preoperative treatment was associated with categorical covariates. Overall survival was calculated from the time of surgery to the date of last contact or the actual date of death documented in the Social Security database or in the medical records. Survival probabilities were estimated using the Kaplan-Meier product-limit method, and groups were compared using the log-rank test. Univariate and multivariate analyses were used to evaluate age, body mass index, and type of chemotherapy. The *t* test was used to analyze the mean age according to the presence or absence of complications. All statistical tests were 2-sided, and significance was set at $P \leq .05$.

RESULTS

Patient Characteristics

We retrospectively analyzed data from 600 consecutive patients. Of these, 409 patients received preoperative treatment (400 patients received preoperative chemoradiation, 8 patients received preoperative chemotherapy, and 1 patient received preoperative radiation therapy). One hundred ninety-one patients (31.83%) underwent primary surgery. Patient characteristics are listed in Table 1. The majority of patients in both groups were Caucasian men, and adenocarcinoma histology predominated (approximately 90%). The gastroesophageal junction was involved in approximately 50% of patients. Pathologic T1 tumors (ypT1) were common in the surgery group (52.4%), whereas ypT3 tumors were common in the preoperative therapy group (28.4%), and all other ypT groups were less frequent than 28.4%. All patients who had any chemotherapy received fluoropyrimidine, and they also received a second cytotoxic (a taxane, a platinum compound, or camptothecin).

Surgical Approaches and Pathologic Stage

Surgical techniques were different between the 2 groups. Among the patients who received preoperative therapy, 64.5% underwent a right transthoracic esophagectomy; however, among the patients who underwent surgery as primary therapy, only 43.5% underwent a right transthoracic esophagectomy. There were similarities in clinical stage (cT) and pathologic stage (ypT) in the primary surgery group (cT1, 52.4%; ypT1, 61.3%); however, but in the preoperative therapy group, there were considerable differences in clinical stage and pathologic stage (cT3 vs ypT3, 78.3% vs 28.4%; cT2 vs ypT2, 18.2% vs 15.9%; cT1 vs ypT1, 1% vs 14.9%; and cT0 vs ypT0, 0% vs 29.6%). This downsizing or downstaging from preoperative therapy (particularly chemoradiation) was not unexpected.[12]

Surgical Complications

Complications from surgery were assessed according to the mean age of patients at risk. The independent-samples *t* test was used to compare means for the 2 groups of patients. The patients in each group were assigned randomly to reduce bias. The older patients had statistically significantly higher rates aspiration pneumonia ($P = .012$), adult respiratory distress syndrome ($P = .005$), cardiovascular complications ($P < .0001$), neurologic

Table 1. Patient Characteristics

Characteristic	No. of Patients (%) Total, N=600	Preoperative Yes, n=409	Preoperative No, n=191	*P**
Age, y				
Median±SD	61±10.5	—	—	
Range	23-84	—	—	
Sex				.040
Men	524 (87.3)	365 (89.2)	159 (83.2)	
Women	76 (12.7)	44 (10.8)	32 (16.8)	
Ethnicity				
Asian	5 (0.8)			
African American	13 (2.2)			
Native American	1 (0.2)			
Hispanic	38 (6.3)			
Caucasian	540 (90)			
Not specified	3 (0.5)			
Tumor location				.128
Upper third of the esophagus	3 (0.5)	1 (0.2)	2 (1)	
Middle third of the esophagus	48 (8)	28 (6.8)	20 (10.5)	
Lower third of the esophagus	240 (40)	160 (39.1)	80 (41.9)	
Gastroesophageal junction	309 (51.5)	220 (53.8)	89 (46.6)	
Clinical T classification				<.001
Tx	3 (0.5)	2 (0.5)	1 (0.5)	
T0	1 (0.2)	0 (0)	1 (0.5)	
Tis	11 (1.8)	0 (0)	11 (5.8)	
T1	104 (17.4)	4 (1)	100 (52.4)	
T2	116 (19.4)	74 (18.2)	42 (22)	
T3	356 (59.4)	320 (78.3)	36 (18.8)	
T4	8 (1.3)	8 (2)	0 (0)	
Clinical N classification				<.001
Nx	4 (0.7)	3 (0.7)	1 (0.5)	
N0	320 (53.4)	156 (38.2)	164 (85.9)	
N1	275 (45.9)	249 (61)	26 (13.6)	
M1	24 (4)	23 (5.6)	1 (0.5)	
Histology				.646
Adenocarcinoma	539 (89.8)	369 (90.2)	170 (89)	
Squamous cell carcinoma	61 (10.2)	40 (9.8)	21 (11)	
ASA risk scale†				.04
Mild systemic disease, no functional limitation	159 (26.5)	99 (24.3)	60 (31.4)	
Severe systemic disease, definite functional limitation	426 (71.10)	304 (74.5)	122 (63.9)	
Severe systemic disease that is constant threat to life	14 (2.3)	5 (1.2)	9 (4.7)	

T indicates tumor classification; Tis indicates tumor in situ; N, lymph node classification; M, metastasis classification; ASA, American Society of Anesthesiology.
*Pearson 2-sided chi-square test or Fisher exact test.
† Available at: http://en.wikipedia.org/wiki/ASA_score accessed September 2008.

complications ($P = .027$), and miscellaneous complications ($P = .011$) (Table 2). None of the other complication categories resulted in rates that were statistically higher in the younger patients.

Impact of Age on Overall Survival by Univariate and Multivariate Analyses

To examine the association between age and overall survival, we conducted univariate and multivariate

Table 2. Postoperative Complications (n=600)

Type of Complication	No.	Mean Age, y	SD, y	*P*
Pulmonary complications	168	61.101	10.162	.733
No pulmonary complications	432	60.775	10.635	
Postoperative aspiration	45	63.933	9.377	.041
No postoperative aspiration	555	60.618	10.551	
Postoperative ARDS	13	52.769	9.338	.005
No postoperative ARDS	587	61.046	10.457	
Postoperative pneumonia	74	59.703	10.354	.309
No postoperative pneumonia	526	61.030	10.516	
Postoperative pulmonary insufficiency	47	61.574	10.208	.631
No postoperative pulmonary insufficiency	553	60.807	10.528	
Postoperative reintubation	37	61.541	10.164	.687
No postoperative reintubation	563	60.822	10.526	
Postoperative tracheostomy	6	62.000	8.922	.791
No postoperative tracheostomy	594	60.855	10.517	
Cardiovascular complications	85	64.847	8.917	<.001
No cardiovascular complications	515	60.210	10.600	
Gastrointestinal complications	109	61.339	10.158	.604
No gastrointestinal complications	491	60.762	10.578	
Postoperative anastomotic leakage	48	62.271	10.214	.334
No postoperative anastomotic leakage	552	60.745	10.521	
Postoperative neurologic complications	26	65.308	10.122	.027
No postoperative neurologic complications	574	60.666	10.478	
Postoperative recurrent laryngeal nerve paresis or paralysis	5	60.800	9.602	.989
No postoperative recurrent laryngeal nerve paresis or paralysis	595	60.867	10.512	
Hematologic complications	81	61.778	9.596	.401
No hematologic complications	519	60.724	10.632	
Postoperative blood transfusions	80	61.863	9.557	.362
No postoperative blood transfusions	520	60.713	10.634	
Postoperative wound complication	102	61.431	9.058	.551
No postoperative wound or infection complication	498	60.751	10.772	
Postoperative wound infection	53	61.491	9.148	.651
No postoperative wound infection	547	60.806	10.624	
Postoperative sepsis	8	59.500	9.928	.711
No postoperative sepsis	592	60.885	10.511	
Postoperative miscellaneous complications	82	63.585	9.970	.011
No postoperative miscellaneous complications	518	60.436	10.523	
Postoperative readmission to the hospital (<30 d)	14	65.214	8.002	.117
No postoperative readmission to the hospital (<30 d)	586	60.763	10.533	
Postoperative readmission to the ICU	33	62.697	10.696	.303
No postoperative readmission to the ICU	567	60.760	10.485	
Reoperation	24	62.875	8.659	.339
No reoperation	576	60.783	10.565	
Postoperative new renal failure (preoperative creatinine ≥2 mg/mL)	5	59.600	7.668	.787
No postoperative new renal failure (preoperative creatinine ≥2 mg/mL)	595	60.877	10.522	
Chylothorax requiring drainage	6	55.833	10.797	.238
No chylothorax requiring drainage	594	60.918	10.491	

SD, standard deviation ARDS, adult respiratory distress syndrome; ICU, intensive care unit.

exploratory analyses using the median age (≤60 years) as the cutoff point (reference for analysis). Patients older than the median age were subgrouped further into 2 groups (ages 61-70 years and aged >70 years).

In the univariate Cox regression analysis, the hazard ratio for death increased with age, and median survival was shortened ($P = .019$) (Table 3). Table 4 lists additional univariate factors that were correlated significantly with overall survival. In the multivariate Cox regression analysis, older age was an independent prognosticator for survival ($P = .041$) (Table 3).

Overall survival was best for the patients aged ≤60 years and was worst for patients aged >70 years; these differences were statistically significant ($P = .018$) (Fig. 1). We also examined the effect of age on overall survival in 2 major cohorts (those who underwent primary surgery and those who received preoperative therapy). Among the patients who underwent primary surgery, those in the

Table 3. Age Subgroups and Survival According to Univariate and Multivariate Analyses

Age Subgroup, y	No. of Patients	P	HR	95% CI	Median Survival, mo
Univariate analysis	600			—	
≤60	286	.019	1.000	—	NR
61-70	193	.048	1.355	1.003-1.831	54.7
>70	121	.008	1.563	1.122-2.177	49.4
Multivariate analysis	600				
≤60	286	.041	1.000	—	NR
61-70	193	.061	1.335	0.987-1.804	54.7
>70	121	.021	1.487	1.062-2.082	49.4

HR indicates hazard ratio; CI, confidence interval; NR, not reached.

Table 4. Univariate Cox Regression Analysis for the Remaining Representative Factors for Survival (n=621)

Factor	Frequency	P	HR	95% CI
Body mass index, kg/m^2		.0016		0.570-0.945
0-25	218		1.000	
>25	405		1.630	
Preoperative therapy		.001		1.380-2.698
No	196		1.000	
Yes	425		1.929	

HR indicates hazard ratio; CI, confidence interval.

group aged >70 years had the worst survival, and the overall comparison was statistically significant (*P* = .022) (Fig. 2). Among the patients who received preoperative therapy, those in the group aged >70 years had the worst survival, and the overall comparison also was statistically significant (*P* = .024) (Fig. 3).

Surgical Mortality and its Impact on Survival of the Entire Population

There were 21 patients who died within 30 days of surgery (19 died in the hospital within 30 days of surgery), and they were included in the calculation of surgical mortality. The overall surgical mortality rate in our series (n = 621) was 3.4%. Table 5 shows the mortality of various age groups. Even when surgical mortality was included in the analysis, patients aged ≤60 years had better survival than patients aged >60 years, and patients aged >70 years had

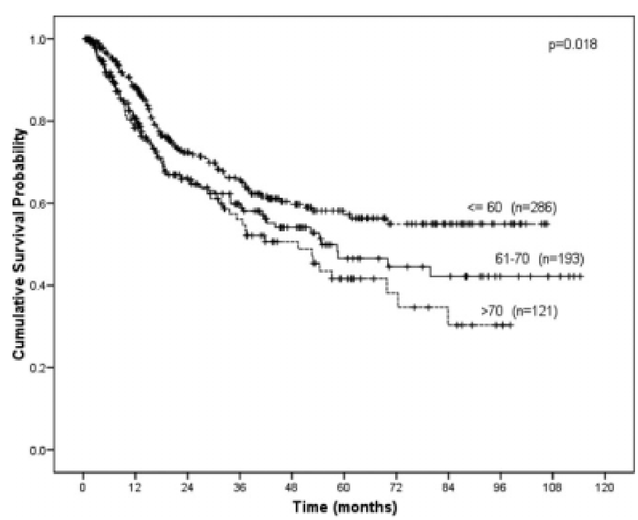

FIGURE 1. This Kaplan-Meier plot illustrates overall survival according to 3 age groups, patients who were the median age (≤60 years) and patients who were older than the median age (subgrouped as ages 61-70 years and aged >70 years), for the entire population (n = 600).

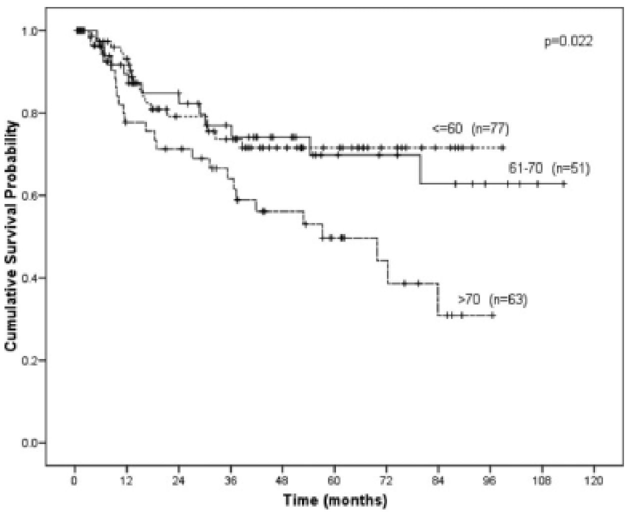

FIGURE 2. This Kaplan-Meier plot illustrates overall survival according to 3 age groups, patients who were the median age (≤60 years) and patients who were older than the median age (subgrouped as ages 61-70 years and aged >70 years), in those who underwent surgery as primary therapy (n = 191).

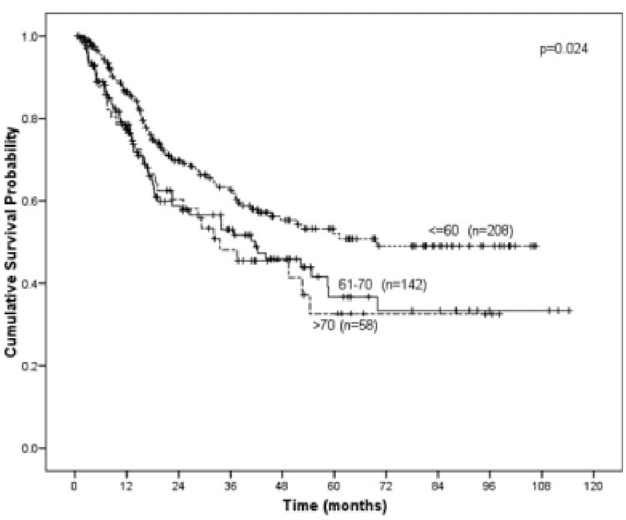

FIGURE 3. This Kaplan-Meier plot illustrates overall survival according to 3 age groups, patients who were the median age (≤60 years) and patients who were older than the median age (subgrouped as ages 61-70 years and aged >70 years), in those who received preoperative therapy (n = 409).

the worst survival trend ($P = .002$) (Fig. 4). Table 6 lists the surgical complications by age group.

Disease-Free Survival

In this study, we were not able to obtain the data on disease-specific mortality, although we did analyze disease-

Table 5. Surgical Mortality (Death Within 30 Days of Surgery) in Various Age Categories (n=621)

Age Group, y	No. of Patients at Risk	No. With Surgical Mortality (% Mortality)
≤60	286	3 (1)
61-70	193	15 (7.7)
>70	121	3 (2.5)

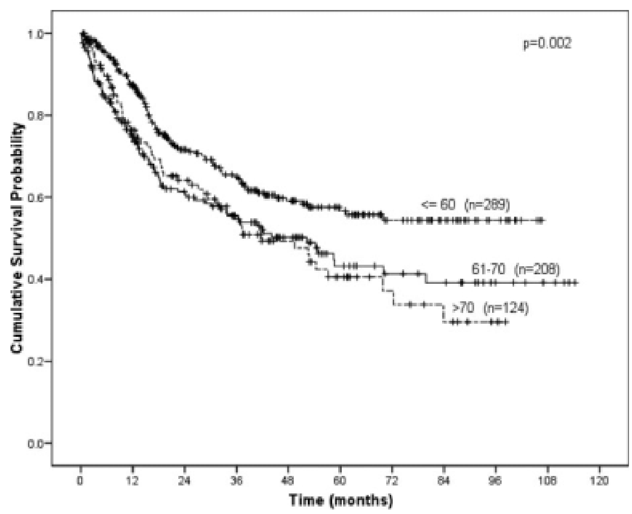

FIGURE 4. This Kaplan-Meier plot illustrates overall survival according to 3 age groups, patients who were the median age (≤60 years) and patients who were older than the median age (subgrouped as ages 61-70 years and aged >70 years), for the population that included 21 patients with surgical mortality (n = 621).

free survival. Figure 5 shows that patients in the older age groups had poor disease-free survival compared with patients aged ≤60 years ($P = .013$)

DISCUSSION

The issues of the impact of age on survival and complications from the surgical procedure in patients with esophageal cancer are far from resolved. A systematic method for evaluating patients' risk for combined-modality therapy or primary surgery has not been implemented globally. Patient morbidity and mortality have been associated with surgical volume.[13-16] However, other factors may need to be examined. Lagarde et al[17-20] have described a model for ranking the risk of postoperative complications and mortality as well as a nomogram. Such models, when

Table 6. Surgical Complication Rates by Age Group (n=621)

Complication	Complication Rate, %			
	Aged ≤60 Years	Ages 61-70 Years	Aged <70 Years	*P*
Pulmonary complications	29.8	26.9	31.5	.045
Aspiration	6.2	7.7	11.3	.180
Pulmonary insufficiency	8.3	8.2	10.5	.060
Pulmonary embolism	0.3	0.5	0.8	.220
Reintubation	6.6	9.6	8.1	.056
Respiratory arrest	0	0.5	0.8	.134
Tracheostomy	0.7	2.4	1.6	.097
Cardiovascular complications	11.1	15.4	25.8	≤.001
Cardiac arrhythmias	7.3	12	21	≤.001
Myocardial infarction	0.3	1.9	1.6	.072
Anastomotic leak	7.6	6.3	11.3	.047
Neurologic complications	2.8	4.8	8.1	.007
Miscellaneous complications	10.7	18.3	20.2	.001

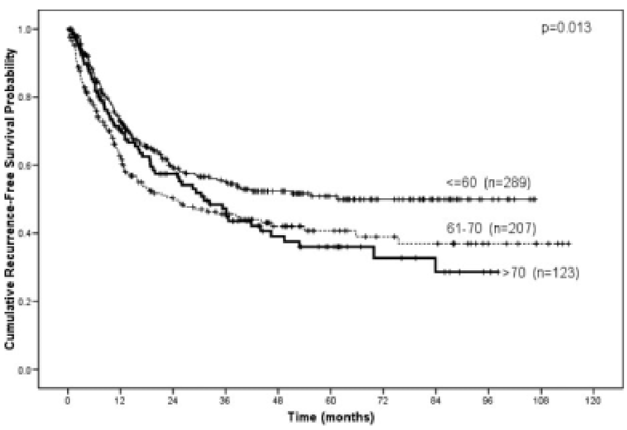

FIGURE 5. This Kaplan-Meier plot illustrates disease-free survival according to 3 age groups, patients who were the median age (≤60 years) and patients who were older than the median age (subgrouped as ages 61-70 years and aged >70 years), for the population that included 21 patients with surgical mortality (n = 621).

executed in a multidisciplinary setting, could be of considerable value in properly selecting the right treatment modality for the right patient. However, prospectively validated models are lacking. In addition, data from large numbers of patients are highly desirable and are not currently available.

Properly selecting patients based on age, comorbid conditions, and tumor characteristics is critical in patients with esophageal cancer, because the therapies can result in severe lifetime problems. Our data suggest that age >70 years imparts significant additional risk from surgery for esophageal cancer. We were particularly interested in long-term survival durations and surgical complications; therefore, we analyzed 600 patients (30-day surgical mortality was not included) without confounding factors. However, when we included 21 patients who had died within 30 days (n = 621), our results continued to support our conclusion that younger patients had the best outcome and older patients (particularly those aged >70 years) had the worst outcome (survival and complications).

Although the strength of our analysis is that we had 600 patients available for analysis, and the data are consistent in 2 major cohorts (those who underwent surgery as primary therapy and those received had preoperative therapy), our analysis suffers from some drawbacks. These include 1) its retrospective nature, because it has all of the inherent weaknesses of such an approach; and 2) a population that, although it is consecutive, is somewhat heterogeneous. Also, we did not have disease-specific survival data available on our patients; however, disease-free survival findings are consistent with our assertion that older patients have a shorter survival after esophageal surgery and that our hypothesis is most likely true. However, our data do support the inclusion of age in future models that may be implemented for patient selection for esophageal cancer surgery. Our data also differ from a report by Lagarde et al,[20] who observed no prognostic impact for age. Our data indicated that older patients (particularly those aged >70 years) have a shorter long-term overall survival after esophagectomy whether or not they received preoperative therapy. Older patients (aged >60 years) also experience more complications and are at risk of higher surgical mortality.

In conclusion, patients with esophageal carcinoma aged >60 years (and particularly those aged >70 years) who underwent definitive surgery had a shorter long-term overall survival (and disease-free survival) and more postoperative complications compared with patients aged ≤60 years. A prospectively testable risk-assessment model is highly desirable and should include age as a variable.

Conflict of Interest Disclosures

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