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Patterns of Care and Treatment Outcomes of Elderly Patients with Stage I Esophageal Cancer: Analysis of the National Cancer Data Base

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ABSTRACT

Introduction: This study analyzes practice patterns, treatment-related mortality, survival, and predictors thereof in elderly patients with early-stage esophageal cancer (EC).

Methods: The National Cancer Data Base was queried for cT1-2 N0 EC in patients 80 years of age and older. Patients were divided into four treatment groups: observation (Obs), chemoradiotherapy (CRT), local excision (LE), and esophagectomy (Eso). Patient, tumor, and treatment parameters were extracted and compared. Analyses were performed on overall survival (OS) and postoperative 30- and 90-day mortality.

Results: A total of 923 patients from 2004 to 2012 were analyzed. Of these, 43% underwent clinical Obs, 22% underwent CRT, 25% underwent LE, and 10% underwent Eso. Patients undergoing Obs were older, had more comorbidities, were treated at nonacademic centers, and lived 25 miles or less from the facility. Patients receiving an operation (Eso or LE) were more often younger, male, white, and in the top income quartile. The postoperative 30-day mortality rates in the LE and Eso groups were 1.3% and 9.6%, respectively ($p < 0.001$) and increased to 2.6% and 20.2% at 90 days, respectively ($p < 0.001$). The 5-year OS rate was 7% for Obs, 20% for CRT, 33% for LE, and 45% for Eso ($p < 0.001$). Multivariate analyses showed improved OS with any local definitive therapy: CRT (hazard ratio [HR] = 0.42, 95% confidence interval [CI]: 0.34–0.52, $p < 0.001$), LE (HR = 0.3, 95% CI: 0.24–0.38, $p < 0.001$), and Eso (HR = 0.32, 95% CI: 0.23–0.44, $p < 0.001$).

Conclusions: There are noteworthy demographic, socioeconomic, and regional disparities influencing management of elderly patients with stage I EC. Despite high rates of Obs, careful consideration of all local therapy options is warranted, given the improved outcomes with treatment.

Keywords: Esophageal cancer; Elderly; Radiotherapy; Esophagectomy; Chemoradiotherapy

Introduction

Esophageal cancer (EC) remains a prevalent oncological disease affecting more than 16,000 people annually within the United States.[1] Despite the best treatment efforts from a multidisciplinary standpoint, 5-year overall survival (OS) is dismally low at 18% for all comers and moderately higher at 41% for the quarter of patients in whom localized cancer confined within the esophagus has been diagnosed.[2] According to National Comprehensive Cancer Network guidelines, a surgical procedure, when feasible, is considered the curative standard of care for stage I cancer.[3] However, various factors such as multiple comorbidities or nonmedical,

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sociodemographic differences may prevent a patient from being managed surgically.[4,5]

Patients with clinically staged T1-2N0 EC comprise a substantially heterogeneous population that has been highly underrepresented or excluded from many phase III trials of trimodality therapy. As such, there are several recommended options for these patients, including esophagectomy (Eso), chemoradiotherapy (CRT), and various surgical techniques of local excision (LE).[3] To date, there have been no randomized trials in this cohort comparing these diverse paradigms; hence, the optimum treatment for this collective remains unclear. Furthermore, several randomized clinical trials have shown that local control and survival of patients with EC directly correlates with the degree of treatment intensity.[6–8] Despite this, older patients with locoregional EC are far less likely to undergo a surgical procedure than younger patients, an observation that is partly attributable to lower rates of referrals to surgeons on the basis of increasing age.[9] Therefore, it appears that physicians may feel more comfortable in providing a less aggressive, nonsurgical therapy such as chemoradiation among the elderly despite their early stage of disease.

Indeed, advanced age presents an added challenge to the health disparities already present in cancer-directed treatment. Elderly patients, a similarly heterogeneous group, may be at higher risk for postoperative complications and death therefrom,[10] which may in turn be influenced by the type of preoperative therapy.[11,12] However, other data have refuted these notions,[13,14] and risk stratification methods have been developed for optimal patient selection, so as to minimize intraoperative and perioperative complications.[15–17]

Hence, because optimal treatment for the very old (≥80 years) patients with stage I EC is highly controversial, we utilized the National Cancer Data Base (NCDB) to investigate practice patterns in this cohort and evaluated outcomes on the basis of four treatment paradigms: Eso, LE, CRT, and observation (Obs). These results have important implications for the evolving management of the rather ambiguous notion of cT1-2N0 disease in an equally ambiguous elderly population.

Material and Methods

This study involved extraction of deidentified patient-level data on locoregional EC cases from the NCDB. The NCDB, a collaborative effort between the American Cancer Society and the Commission on Cancer of the American College of Surgeons, is a comprehensive oncology surveillance program that captures approximately 70% of all new cancer diagnoses in the United States from more than 1500 Commission on Cancer–approved centers.[18] Data reporting to the NCDB is strictly regulated.[19] The NCDB file was awarded to the authors for analytical purposes and is exempt from institutional review board review.

The inclusion criteria encompassed elderly patients (≥80 years) in whom primary (nonmetastatic) cT1-2N0 EC had been diagnosed from 2004 to 2012. Per the NCDB participant user files, the seventh edition American Joint Commission on Cancer staging system was reportedly used to stage patients whose disease was diagnosed in 2010 or later, whereas the sixth edition was used for cases from 2009 or earlier. Therefore, the only patients with cT2 allowed were from 2010–2012. Our study was further restricted to patients categorized as having undergone clinical Obs or having received local definitive therapy consisting of concurrent CRT, LE, or Eso. Obs was defined as not having received any systemic therapy, radiation therapy, or operation. The CRT group consisted of patients who received concurrent CRT with or without induction chemotherapy, with the former defined as chemotherapy started within 14 days of the start of radiation therapy (91% of patients). A minor subset of patients in the CRT group (n = 15) underwent a local excision within 100 days before CRT. This was allowed because the timing suggested CRT as part of the initial definitive therapy, such as for positive margins. The LE group consisted of patients who had undergone any form of local tumor excision or destruction that did not constitute a partial or total Eso. Eso was defined as partial or total removal of the esophagus with or without a gastrectomy. Patients in the Eso group could receive neoadjuvant or adjuvant therapy, although this pertained to less than 10% of cases. Finally, we excluded patients with unknown survival status or timing of specific therapies delivered, as well as patients treated with a "palliative intent," as they likely received lower doses of radiation or chemotherapy for symptomatic management.

Information collected on each patient broadly included demographic data, comorbidity scores as adapted by Deyo et al.,[20] clinicopathologic tumor parameters, and treatment variables. Of note, facility type was dichotomized into academic/research versus nonacademic facilities (consisting of community cancer programs or comprehensive community cancer programs). Patient distance from facility was also dichotomized to either local (0–25 miles) and distant (>25 miles) distances. Facility volume, which was studied in the Eso group, was calculated as the total number of Esos performed in a given facility from 2004 to 2012, regardless of disease stage.

Statistical analysis was performed with SAS software, version 9.4 (SAS Institute, Inc., Cary, NC). α Values less than 0.05 were considered significant; all tests were two sided. Comparisons of sociodemographic, tumor, and treatment characteristics by group were performed with chi-square or Fisher's exact tests. Post hoc analysis involved pairwise comparisons using the z test of two proportions with a Bonferroni correction. The Kruskal-Wallis test was utilized to detect statistically significant differences in the median age between the four treatment groups. Two binomial logistic regression models were then constructed to ascertain the effects of various patient, tumor, and treatment characteristics on the likelihood of being observed (versus any form of local therapy) or the likelihood of undergoing an operation (versus CRT or Obs). ORs with corresponding 95% confidence intervals (CIs) were reported, and both logistic regression models were statistically significant, with $R^2 = 18\%$ to 24% and $R^2 = 30\%$ to 41.5%, respectively.

The primary outcome of interest was OS, which was defined as the time from diagnosis to last contact or death. OS time for surviving patients was censored at the time of last contact, and 5-year OS was estimated by the Kaplan-Meier method. A Cox proportional hazards model was used to study the effects of several factors on survival, expressed as hazard ratios (HRs). Only variables significant on univariable analysis were included in the multivariable analysis.

Results

Patterns of Care

A CONSORT diagram of patient selection is provided in Figure 1. The study population comprised 923 patients (Table 1). Of these, 43% underwent clinical Obs, 22% underwent CRT, 25% underwent LE, and 10% underwent Eso. The median age was 84 years (range 80–90 years) for the overall cohort and significantly lower in the Eso group than in the Obs group (82 years versus 85 years [$p < 0.001$]). Patients were predominately male and white; however, the highest proportions of women and African Americans were found in the nonsurgical groups (Obs or CRT [$p < 0.001$]). Roughly 70% of the elderly population had a comorbidity score of 0, out of which 38.5% were observed. Comorbidity score distribution was significantly different only between the Obs and LE groups ($p < 0.001$) and between the Obs and CRT groups ($p = 0.004$), despite Obs and Eso having similar distributions with overall lower scores of 0 (63.1% and 64.9%, respectively). Surgical interventions were mainly performed at academic centers. Adenocarcinomas were more common than squamous cell carcinomas (68% versus 22.4%), which correlated with a prevalent tumor location within the lower third of the esophagus (60.9%). Eso and LE were more often used in patients with adenocarcinomas (Fig. 2).

On binomial logistic regression to predict the likelihood of a particular treatment within the elderly population (Table 2), there were significantly higher odds of undergoing clinical Obs with increasing age (OR = 1.18, 95% CI: 1.13–1.23, $p < 0.001$), a comorbidity score of 2 or higher (OR = 2.36, 95% CI: 1.36–4.12, $p = 0.002$),

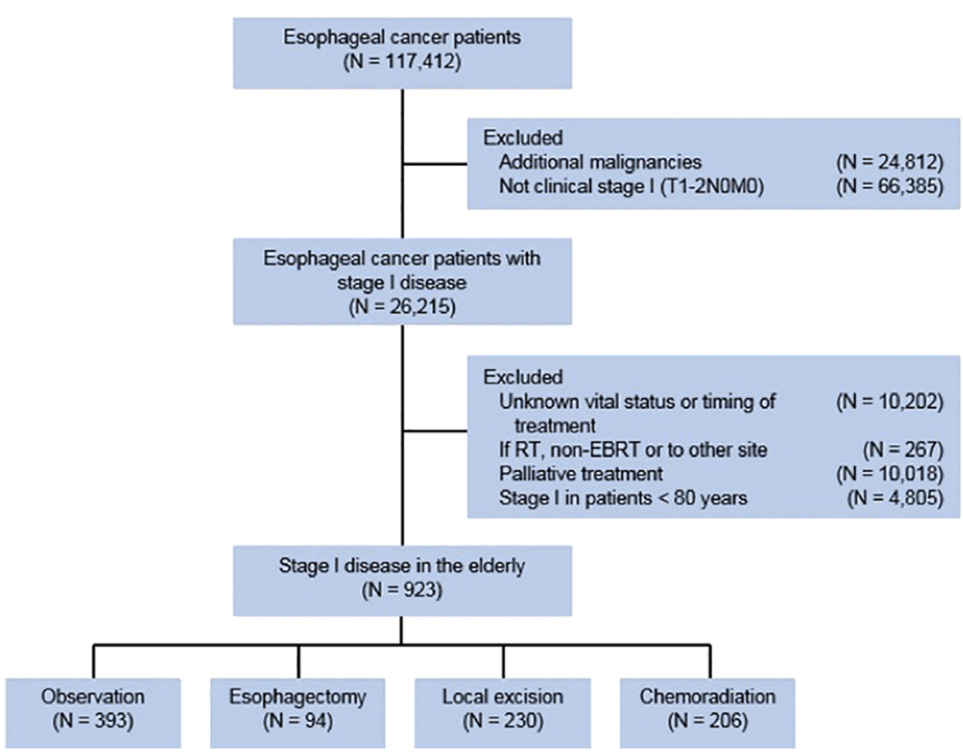

Figure 1. CONSORT diagram. EBRT, external beam radiation therapy; RT, radiation therapy.

Table 1. Baseline Patient Demographics and Clinical and Tumor Characteristics

Factor	Overall (N = 923 [100%])	Obs (n = 393 [43%])	CRT (n = 206 [22%])	LE (n = 230 [25%])	Eso (n = 94 [10%])	*p* Value
Age at diagnosis, y						
Median	84	85	83	84	82	<0.001
Range	80-90	80-90	80-90	80-90	80-90	
Sex						
Male	611 (66.2)	235 (59.8)	136 (66)	168 (73)	72 (76.6)	<0.001
Female	312 (33.8)	158 (40.2)	70 (34)	62 (27)	22 (23.4)	
Race						
White	857 (92.8)	359 (91.3)	191 (92.7)	217 (94.3)	90 (95.7)	<0.001
Black	34 (3.7)	20 (5.1)	11 (5.3)	<10 (0)	<10 (3.2)	
Other	32 (3.5)	14 (3.6)	<10 (1.9)	13 (5.7)	<10 (1.1)	
Comorbidity score						
0	645 (70)	248 (63.1)	153 (74.3)	183 (79.6)	61 (64.9)	<0.001
1	203 (22)	100 (25.5)	44 (21.3)	35 (15.2)	24 (25.5)	
≥2	75 (8)	45 (11.4)	<10 (4.4)	12 (5.2)	<10 (9.6)	
Median household income						
<$30,000 (bottom quartile)	79 (8.6)	36 (9.2)	17 (8.2)	15 (6.5)	11 (11.7)	<0.001
$30,000-$34,999	161 (17.4)	70 (17.8)	49 (23.8)	33 (14.3)	<10 (9.6)	
$35,000-$45,999	266 (28.8)	113 (28.7)	56 (27.2)	65 (28.3)	32 (34)	
≥$46,000 (top quartile)	376 (40.7)	161 (41)	69 (33.5)	107 (46.5)	39 (41.5)	
Unknown	41 (4.4)	13 (3.3)	15 (7.3)	10 (4.4)	<10 (3.2)	
Insurance						
Uninsured	10 (1.1)	5 (1.3)	<10 (0)	<10 (1.3)	<10 (2.1)	<0.001
Private	79 (8.5)	30 (7.6)	16 (7.8)	26 (11.3)	<10 (7.5)	
Medicaid	<10 (0.8)	<10 (0)	<10 (2.4)	<10 (0.9)	<10 (0)	
Medicare	804 (87.1)	346 (88)	182 (88.3)	194 (84.3)	82 (87.2)	
Other government	<10 (0.8)	<10 (0.8)	<10 (0.5)	<10 (1.3)	<10 (0)	
Unknown	16 (1.7)	<10 (2.3)	<10 (1)	<10 (0.9)	<10 (3.2)	
Community type						
Metro county	755 (81.8)	327 (83.2)	173 (84)	177 (77)	78 (83)	0.25
Urban county	114 (12.4)	50 (12.7)	21 (10.2)	36 (15.6)	<10 (7.4)	
Rural	17 (1.8)	<10 (1.3)	<10 (1.9)	<10 (2.2)	<10 (3.2)	
Unknown	37 (4)	11 (2.8)	<10 (3.9)	12 (5.2)	<10 (6.4)	
Tumor location (esophagus)						
Upper third	51 (5.5)	25 (6.4)	15 (7.3)	<10 (3.9)	<10 (2.1)	<0.001
Middle third	149 (16.1)	61 (15.5)	34 (16.5)	50 (21.7)	<10 (4.3)	
Lower third	562 (60.9)	218 (55.5)	120 (58.2)	141 (61.3)	83 (88.3)	
Other/unknown	161 (17.4)	89 (22.6)	37 (18)	30 (13)	<10 (5.3)	
Histological subtype						
Adenocarcinoma	628 (68)	237 (60.3)	130 (63.1)	188 (81.7)	73 (77.7)	<0.001
Squamous cell	207 (22.4)	112 (28.5)	66 (32)	17 (7.4)	12 (12.8)	
Other	88 (9.6)	44 (11.2)	10 (4.9)	25 (10.9)	<10 (9.5)	
Facility type						
Academic/research	394 (42.7)	98 (24.9)	66 (32)	170 (73.9)	60 (63.8)	<0.001
Nonacademic	529 (57.3)	295 (75.1)	140 (68)	60 (26.1)	34 (36.2)	
Distance from facility						
0-25 miles	655 (71)	328 (83.5)	164 (79.6)	109 (47.4)	54 (57.4)	<0.001
>25 miles	243 (26.3)	56 (14.2)	34 (16.5)	116 (50.4)	37 (39.4)	
Unknown	25 (2.7)	<10 (2.3)	<10 (3.9)	<10 (2.2)	<10 (3.2)	
Surgical margin	*923* surgical:		*15* surgical:			
Negative	189 (20.5)	No surgery	<10 (20)	99 (43)	87 (92.5)	<0.001
Positive	43 (4.6)		<10 (53.3)	32 (13.9)	<10 (3.2)	
Unknown	691 (74.9)		<10 (26.7)	99 (43)	<10 (4.3)	

CRT, chemoradiation; Eso, Esophagectomy; Obs, observation; LE, local excision.

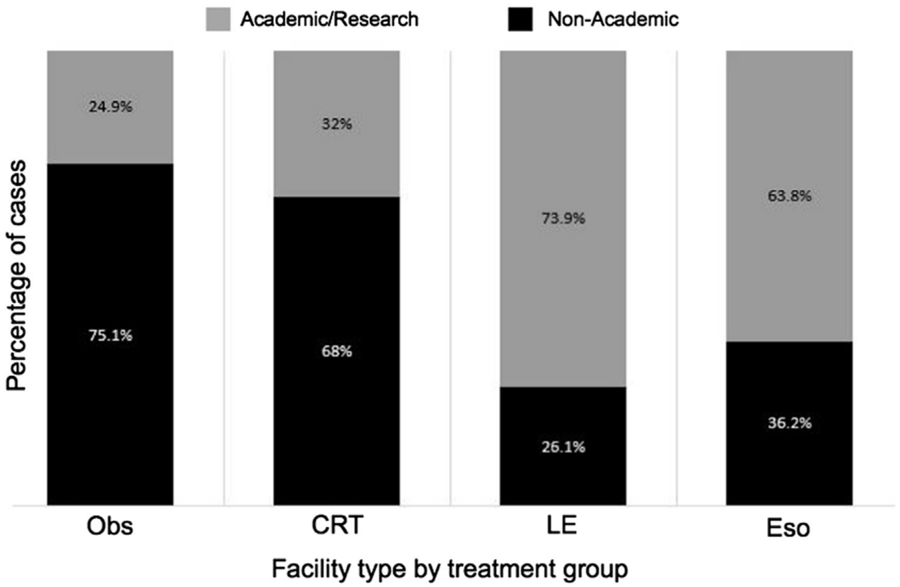

Figure 2. Treatment by facility type. CRT, chemoradiotherapy; Eso, esophagectomy; LE, local excision; Obs, observation.

treatment at a nonacademic center (OR = 3.1, 95% CI: 2.25–4.28, $p < 0.001$), and residence within 25 miles of the facility (OR = 2.1, 95% CI: 1.44–4.28, $p < 0.001$). Conversely, factors associated with increased likelihood of undergoing an operation (LE or Eso) included lower age ($p < 0.001$), male sex ($p = 0.007$), white race ($p = 0.016$), treatment at an academic center ($p < 0.001$), and living more than 25 miles from the facility ($p < 0.001$). Being in the top income quartile was the most notable association with undergoing and operation (OR = 2.24, 95% CI: 1.12–4.49, $p = 0.023$).

Treatment Outcomes

The 30- and 90-day mortality rates were evaluated in both surgical groups, recognizing that 40 patients in the LE group (17%) lacked this information. The 30-day mortality was 1.3% in the LE group (n = 3) (1.5% when unknown values were excluded) and 9.6% in the Eso group (n = 9) ($p < 0.001$). These numbers increased to 2.6% (n = 6) and 20.2% (n = 19), respectively, at 90 days ($p < 0.001$). Given the comparatively high post-operative deaths in the Eso group, facility volume as a potential associative factor was then investigated for this population. Of the 60 patients treated at an academic/research center, 58 (97%) were at a center performing surgery more than 25 during the study time period, as compared with 18 of the 34 patients (53%) treated at a nonacademic facility. OS was significantly higher when patients were treated at institutions performing surgery in more than 25 cases over the time period ($p = 0.015$). However, there did not seem to be a significant association between 30-day mortality and facility type ($p = 0.734$) or volume ($p = 0.117$).

Survival Analysis

The median follow-up for all patients was 13.9 months (range 0–119.8 months). Figure 3 displays survival curves for each of the four groups. The 5-year OS estimates were 7% for Obs, 20% for CRT, 33% for LE, and 45% for Eso ($p < 0.001$).

Factors associated with improved OS on univariable analysis included treatment group, age, comorbidity score, sex, facility type, distance from facility, and year of diagnosis. Histological subtype was not a significant factor on univariate analysis. On multivariate Cox regression analysis (Table 3), all factors with the exception of sex and year of diagnosis remained statistically significant. Any form of local therapy was significantly superior to Obs in terms of OS (CRT HR = 0.42, 95% CI: 0.34–0.52; LE HR = 0.3, 95% CI: 0.24–0.38; and Eso HR = 0.32, 95% CI: 0.23–0.44 [all $p < 0.001$]). Intercohort comparisons of HRs showed no significant association between the two surgical groups. However, CRT trended toward worse OS compared with Eso (HR = 1.3, 95% CI: 0.92–1.82; $P = 0.109$) and was significantly worse than LE (HR = 1.4, 95% CI: 1.08–1.83; $P = 0.012$).

Discussion

Although the median age of patients in whom EC has been diagnosed is around 67 years, very elderly patients represent a unique and challenging subpopulation to health care providers for a variety of reasons. Apart from known factors that are often associated with treatment disparities such as socioeconomic status or ethnicity,[4,5] the age of these patients in itself predisposes them to being potentially deprived of consideration of all treatment options. In the largest retrospective study to date

Table 2. Binary Logistic Regression Predicting Observation and Surgery

Variable	OR (95% CI)	OR *p* Value	Type 3 *p* Value
Model predicting observation vs. local therapy			
Age (1-y increment)	1.18 (1.13-1.23)	<0.001	<0.001
Comorbidity score			
0	1		0.007
1	1.27 (0.89-1.82)	0.187	
≥2	2.36 (1.36-4.12)	0.002	
Facility type			
Academic/research	1		<0.001
Nonacademic	3.1 (2.25-4.28)	<0.001	
Distance from facility			
0-25 miles	2.1 (1.44-4.28)	<0.001	<0.001
>25 miles	1		
Model predicting surgery vs. nonsurgical/observation			
Age (1-y increment)	0.9 (0.85-0.95)	<0.001	<0.001
Sex			
Male	1		0.007
Female	0.6 (0.41-0.87)	0.007	
Race			
White	1		0.046
Black	0.19 (0.05-0.73)	0.016	
Other	1.3 (0.52-3.23)	0.574	
Median household income			
<$30,000 (bottom quartile)	1		0.003
$30,000-$34,999	0.88 (0.42-1.86)	0.738	
$35,000-$45,999	1.85 (0.92-3.71)	0.083	
≥$46,000 (top quartile)	2.24 (1.12-4.49)	0.023	
Tumor location			
Unknown	0.4 (0.24-0.66)	<0.001	0.002
Upper third	0.47 (0.21-1.07)	0.071	
Middle third	0.7 (0.44-1.13)	0.147	
Lower third	1		
Facility type			
Academic/research	1		<0.001
Nonacademic	0.19 (0.13-0.27)	<0.001	
Distance from facility			
0-25 miles	0.25 (0.17-0.38)	<0.001	<0.001
>25 miles	1		
Year of diagnosis			
2004	1		0.009
2005	1.51 (0.57-3.95)	0.405	
2006	0.64 (0.24-1.7)	0.375	
2007	2.49 (1.04-5.93)	0.04	
2008	2.92 (1.23-6.93)	0.015	
2009	2.13 (0.89-5.11)	0.09	
2010	2.47 (1.1-5.54)	0.028	
2011	2.45 (1.07-5.6)	0.034	
2012	2.48 (1.07-5.77)	0.035	

CI, confidence interval.

of patients 80 years or older in whom stage I EC has been diagnosed, we have shown that most patients received no form of local therapy at all for their potentially curable disease, whereas 22% were treated with CRT, 25% with local resection of their tumors, and 10% with an Eso. The 5-year OS was not surprisingly poor with Obs; however, these patients were more likely to have two or more significant comorbidities, and they also exhibited the sharpest decline in survival from time of diagnosis, which is likely attributable to non–cancer-related deaths.

In general, health disparities were observed herein and are important to characterize. When the elderly were stratified by any surgical procedure versus CRT or Obs, female patients, African Americans, and patients of the bottom income quartile were less likely to undergo surgery—findings that corroborate the results from other retrospective studies in nonelderly cohorts.[21,22] Another key factor that drives the treatment of choice and subsequent outcome is the type of treating facility. Although slightly more than half of all patients were treated within the community, 82% of these patients did not undergo an operation (compared with 42% of patients treated in an academic center). A possible explanation for this difference is a higher dependence on direct referrals in the community. For example, when Steyerberg et al.[9] utilized the Surveillance, Epidemiology, and End Results database to analyze referral patterns in elderly patients 65 years or older in whom locoregional EC had been diagnosed, they discovered that older patients were far less likely to be referred to a surgeon (61% for age ≥85 years versus 80% for ages 65–75) and were therefore also less likely to undergo an operation (23% for age ≥85 years versus 55% for ages 65–70). Lastly, there was a rather compelling finding that patients living closer to treating institutions tended to undergo Obs. Likely reasons include the clinical judgment that observing patients who live locally are potentially easier to observe regularly or that some patients were medically unfit to endure repeated visits to an institution farther from home.

Despite health disparities among the elderly, there are valid high-risk features that make any patient a poor surgical candidate. Major morbidities such as anastomotic leakage, sepsis, pneumonia, and prolonged ventilation are feared after an Eso, with rates documented to be as high as 50%.[23–25] Similarly, 30-day mortality can range from 1.4% to 9.8%,[26,27] with advances in surgical technique and postoperative care likely accounting for the improved perioperative outcomes.[28] Patients in our Eso group had a 30-day mortality rate of 9.6%, which is high but within the realm of historical rates. However, this number doubled at 90 days, which is concerning and argues for better patient selection, even more so for patients 80 years or older because older age has been found to be a negative predictor of outcomes.[17,27] Eso was associated with the highest 5-year OS (45%);

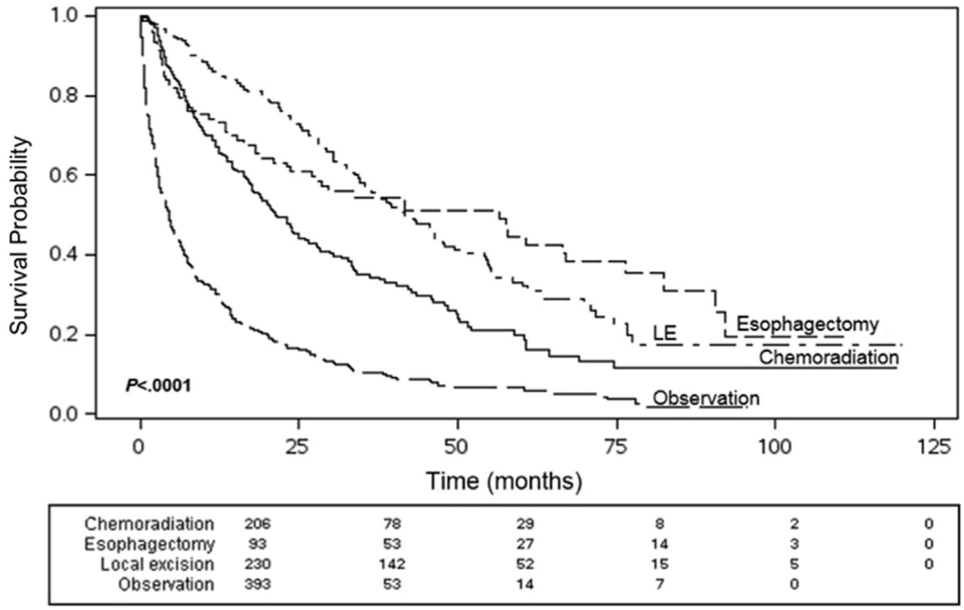

Figure 3. Kaplan-Meier overall survival curve as stratified for treatment group. LE, local excision.

however, the survival benefit must be carefully balanced with the potential perioperative complications on a case-by-case basis. We suggest that patients be categorized as either "functionally fit" or "functionally unfit" instead of by age through the use of performance status and geriatric assessments (in addition to comorbidity evaluation) to expound on the risks and benefits of Eso.[29] Surgery at a high-volume facility is also recommended on the basis of prior studies,[15] with our findings of 25 or fewer cases per facility being associated with significantly worse survival.

Table 3. Multivariable Analysis of Predictors of Overall Survival

Variable	Hazard Ratio (95% CI)	*p* Value
Treatment group		
Observation	1	
Chemoradiation	0.42 (0.34-0.52)	<0.001
Local excision	0.3 (0.24-0.38)	<0.001
Esophagectomy	0.32 (0.23-0.44)	<0.001
Age (1-y increment)	1.08 (1.06-1.11)	<0.001
Comorbidity score		
0	1	
1	1.4 (1.15-1.69)	<0.001
≥2	2.3 (1.69-3.02)	<0.001
Facility type		
Academic/research	1	
Nonacademic	1.22 (1.01-1.46)	0.037
Distance from facility		
0-25 miles	1.36 (1.1-1.67)	<0.001
>25 miles	1	
Sex		
Male	1	0.217
Female	1.12 (0.94-1.33)	
Year of diagnosis	NS	NS

CI, confidence interval; NS, not significant.

Although less invasive than Eso, LE is considered a surgical procedure that may consist of various local therapy modalities such as endoscopic mucosal resection, radiofrequency ablation, cryotherapy, and photodynamic therapy. Such therapies have been shown to be both safe and effective for management of early EC.[30–32] In our cohort, there were no significant differences in comorbidity scoring between LE or Eso. Negative margins were more likely after Eso, but LE was associated with lower rates of 30- and 90-day mortality (1.3% and 2.6%, respectively). However, we must interpret these data with caution, largely owing to the proportion of missing values with regard to margin status and mortality. Pairwise comparisons showed significant improvement in OS with LE over CRT but no statistically significant difference between LE and Eso. Therefore, LE should be considered as an optimal treatment strategy among the elderly.

For patients who are unable to tolerate any form of surgery, concurrent CRT might provide a survival benefit over Obs alone (5-year OS of 20% versus 7% [$p < 0.001$]). Although the toxicity profile of CRT should be cautiously considered in older patients, several measures can be taken to limit possible acute and long-term adverse effects. In particular, advances in radiation delivery and techniques such as intensity-modulated radiotherapy and charged particle therapy (carbon ion or proton beam therapy) are slowly improving outcomes and replacing the current standard of three-dimensional conformal radiotherapy.[33–35] Lin et al. have demonstrated several benefits with the utilization of intensity-modulated radiotherapy in patients with EC, including lower all-cause mortality (HR = 0.83, 95% CI: 0.72–0.95), cardiac mortality (HR = 0.18, 95% CI: 0.06–0.54), and other-cause mortality (HR = 0.54, 95% CI: 0.35–0.84).[12,36] Randomized studies are required, however, to obtain a deeper understanding of the maximum benefit of CRT delivered through advanced radiation techniques in patients 80 years of age and older.

As with any retrospective analysis, our study is largely hindered by an undisputable selection bias that cannot be fully taken into consideration outside of a randomized trial setting. That being said, we were able to account for several important patient, tumor, and treatment characteristics such as age, comorbidity scoring, facility type, and distance, all of which remained significant predictors of OS in our multivariate analysis. Further limiting factors in our study include lack of information regarding performance status, staging modality (whether by diagnostic imaging or endoscopic evaluation), chemotherapy regimens, radiation dose distribution and modality, perioperative complications, disease-free survival, and non–cancer-specific causes of death.

In conclusion, we have demonstrated that a surprisingly large proportion of patients 80 years and older with stage I EC remain under clinical Obs after their diagnosis. Any form of local therapy, including CRT, statistically improved OS when compared with Obs. Finally, if surgery is feasible, local excision should be considered over CRT and Eso, given the potentially lower toxicity profile and postoperative mortality rates.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66:7-30.
2. National Cancer Institute Surveillance, Epidemiology, and End Results Program. SEER stat fact sheets. esophageal cancer. http://seer.cancer.gov/statfacts/html/esoph.html. Accessed October 10, 2016.
3. National Comprehensive Cancer Network. Esophageal and esophagogastric junction cancers (version 2. 2016). https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed October 11, 2016.
4. Wang N, Cao F, Liu F, et al. The effect of socioeconomic status on health-care delay and treatment of esophageal cancer. *J Transl Med*. 2015;13:241.
5. Revels SL, Morris AM, Reddy RM, Akateh C, Wong SL. Racial disparities in esophageal cancer outcomes. *Ann Surg Oncol*. 2013;20:1136-1141.
6. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol*. 2015;16:1090-1098.
7. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol*. 2008;26:1086-1092.
8. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA*. 1999;281:1623-1627. http://www.ncbi.nlm.nih.gov/pubmed/10235156. Accessed October 29, 2016.
9. Steyerberg EW, Neville B, Weeks JC, Earle CC. Referral patterns, treatment choices, and outcomes in locoregional esophageal cancer: a population-based analysis of elderly patients. *J Clin Oncol*. 2007;25:2389-2396.
10. Markar SR, Low DE. Physiology, not chronology, dictates outcomes after esophagectomy for esophageal cancer: outcomes in patients 80 years and older. *Ann Surg Oncol*. 2013;20:1020-1026.
11. Mak RH, Mamon HJ, Ryan DP, et al. Toxicity and outcomes after chemoradiation for esophageal cancer in patients age 75 or older. *Dis esophagus*. 2010;23:316-323.
12. Lin SH, Zhang N, Godby J, et al. Radiation modality use and cardiopulmonary mortality risk in elderly patients with esophageal cancer. *Cancer*. 2016;122:917-928.
13. Ruol A, Portale G, Zaninotto G, et al. Results of esophagectomy for esophageal cancer in elderly patients: age has little influence on outcome and survival. *J Thorac Cardiovasc Surg*. 2007;133:1186-1192.
14. Ruol A, Portale G, Castoro C, et al. Effects of neoadjuvant therapy on perioperative morbidity in elderly patients undergoing esophagectomy for esophageal cancer. *Ann Surg Oncol*. 2007;14:3243-3250.
15. Steyerberg EW, Neville BA, Koppert LB, et al. Surgical mortality in patients with esophageal cancer: development and validation of a simple risk score. *J Clin Oncol*. 2006;24:4277-4284.
16. Wright CD, Kucharczuk JC, O'Brien SM, Grab JD, Allen MS. Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk adjustment model. *J Thorac Cardiovasc Surg*. 2009;137:587-596.
17. Ferguson MK, Celauro AD, Prachand V. Prediction of major pulmonary complications after esophagectomy. *Ann Thorac Surg*. 2011;91:1494-1501.
18. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol*. 2008;15:683-690.
19. American College of Surgeons. Participant user files. https://www.facs.org/quality-programs/cancer/ncdb/puf. Accessed March 12, 2017.
20. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45:613-619.
21. Steyerberg EW, Earle CC, Neville BA, Weeks JC. Racial differences in surgical evaluation, treatment, and outcome of locoregional esophageal cancer: a population-based analysis of elderly patients. *J Clin Oncol*. 2005;23:510-517.

22. Dubecz A, Sepesi B, Salvador R, et al. Surgical resection for locoregional esophageal cancer is underutilized in the United States. *J Am Coll Surg*. 2010;211:754–761.
23. Bailey SH, Bull DA, Harpole DH, et al. Outcomes after esophagectomy: a ten-year prospective cohort. *Ann Thorac Surg*. 2003;75:217–222 [discussion 222].
24. Urschel JD. Esophagogastrostomy anastomotic leaks complicating esophagectomy: a review. *Am J Surg*. 1995;169:634–640.
25. Whooley BP, Law S, Alexandrou A, Murthy SC, Wong J. Critical appraisal of the significance of intrathoracic anastomotic leakage after esophagectomy for cancer. *Am J Surg*. 2001;181:198–203.
26. Raymond DP, Seder CW, Wright CD, et al. Predictors of major morbidity or mortality after resection for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk adjustment model. *Ann Thorac Surg*. 2016;102:207–214.
27. Law S, Wong K-H, Kwok K-F, Chu K-M, Wong J. Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. *Ann Surg*. 2004;240:791–800.
28. Li J, Shen Y, Tan L, et al. Is minimally invasive esophagectomy beneficial to elderly patients with esophageal cancer? *Surg Endosc*. 2015;29:925–930.
29. Tougeron D, Hamidou H, Scotté M, et al. Esophageal cancer in the elderly: an analysis of the factors associated with treatment decisions and outcomes. *BMC Cancer*. 2010;10:510.
30. Berry MF, Zeyer-Brunner J, Castleberry AW, et al. Treatment modalities for T1N0 esophageal cancers: a comparative analysis of local therapy versus surgical resection. *J Thorac Oncol*. 2013;8:796–802.
31. Soetikno R. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. *J Clin Oncol*. 2005;23:4490–4498.
32. Galey KM, Wilshire CL, Watson TJ, et al. Endoscopic management of early esophageal neoplasia: an emerging standard. *J Gastrointest Surg*. 2011;15:1728–1735.
33. Lin SH. The utility of proton beam therapy with concurrent chemotherapy for the treatment of esophageal cancers. *Cancers (Basel)*. 2011;3:4090–4101.
34. Verma V, Lin SH, Simone CB, Mehta MP. Clinical outcomes and toxicities of proton radiotherapy for gastrointestinal neoplasms: a systematic review. *J Gastrointest Oncol*. 2016;7:644–664.
35. Chuong MD, Hallemeier CL, Jabbour SK, et al. Improving outcomes for esophageal cancer using proton beam therapy. *Int J Radiat Oncol Biol Phys*. 2016;95:488–497.
36. Lin SH, Wang L, Myles B, et al. Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs intensity-modulated radiotherapy for esophageal cancer. *Int J Radiat Oncol Biol Phys*. 2012;84:1078–1085.