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Higher clinical suspicion is needed for prompt diagnosis of esophageal adenocarcinoma in young patients

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Abstract

Background: Esophageal cancer is considered a disease of the elderly. Although the incidence of esophageal adenocarcinoma in young patients is increasing, guidelines for endoscopic evaluation of gastroesophageal reflux disease and Barrett's esophagus include age as a cutoff. There is a paucity of data on the presentation and treatment of esophageal cancer in young patients. Most studies are limited by small sample sizes and conflicting findings are reported regarding delayed diagnosis and survival compared to older patients.

Methods: A retrospective cohort study was performed utilizing the National Cancer Database between 2004 and 2015. Patients with esophageal adenocarcinoma were divided into quartiles by age (18–57, 58–65, 66–74, 75+) for comparison. Clinicopathologic and treatment factors were compared between groups.

Results: 101,596 patients were identified with esophageal cancer. The youngest patient group (18–57 years) had the highest rate of metastatic disease (37%). No difference in tumor differentiation was observed between age groups. Younger patient groups were more likely to undergo treatment despite advanced stage at diagnosis. Overall 5-year survival was better for younger patients with local disease, but the difference was less pronounced in locoregional and metastatic cases.

Conclusion: In this study, young patients were more likely to have metastatic disease at diagnosis. Advanced stage in young patients may reflect the need for more aggressive clinical evaluation in high-risk young patients.

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INTRODUCTION

Esophageal cancer is the 8th most common cancer worldwide and the 6th most common cause of cancer-related death.[1] Although considered a highly fatal disease, therapeutic advancements have resulted in improved 5-year overall survival from 5.1% to 19.2% over the last four decades.[2, 3]

Esophageal cancer occurs primarily in the 6th and 7th decades of life; as such, it is considered a disease of the elderly. However, esophageal cancer does occur in young patients and patients younger than 55 years currently account for almost 13% of new diagnoses in the United States.[3] Citing low risk of disease in young patients, current guidelines from the American College of Gastroenterology and American Gastroenterologic Association recommend against endoscopy for evaluation of dyspepsia in patients <60 years old, even in the setting of alarm symptoms.[4] (Table 1) Furthermore, guidelines specify that age > 50 is considered a high risk indication for endoscopic evaluation of gastroesophageal reflux symptoms or to screen for Barrett's Esophagus[5–9] Similarly, national guidelines in other western countries recommend against urgent endoscopic evaluation of dyspepsia in patients age <55.[10, 11] This is concerning as studies suggest that the incidence of esophageal cancer among young patients is increasing.[12, 13] Furthermore, perceptions of esophageal cancer as a rare disease in young patients may result in lower clinical suspicion; as such, some studies have suggested that patients <50 years old are more likely to have delayed diagnosis and consequently, more advanced disease.[14–18] Given that 5-year overall survival for advanced disease is <25% and <5% for regional and distant disease, respectively, earlier identification has a significant impact on prognosis.[3]

To date, esophageal cancer in young patients has received minimal attention in the literature. Most studies are single-institution experiences limited by small sample sizes and conflicting findings relating to the presentation, treatment and prognosis of this population; as such, the clinicopathologic presentation and outcomes of esophageal cancer in young patients is not well defined.[14–25] Further complicating current understanding of this disease in young patients is the lack of consensus as to what constitutes a "young patient", with many studies arbitrarily selecting age under 50.[14–21]

Given that survival for this disease remains poor, esophageal cancer in young patients merits further investigation to better guide diagnosis and management in this population. The purpose of this study was to compare the clinicopathologic characteristics and survival of patients with esophageal cancer between age groups utilizing a national cancer cohort in the United States.

METHODS

Data Source and Study Population

A population-based retrospective review was performed using data from the National Cancer Database (NCDB) Participant User File (PUF). All patients diagnosed between 2004 to 2015 with adenocarcinoma of the esophagus (ICD-0 Code C15.0–15.9) and esophagogastric junction (C16.0, cardia NOS) with a single primary malignancy were included. The NCDB

is a cancer registry from the American College of Surgeons and American Cancer Society which collects data from more than 1,500 Commission on Cancer accredited centers. (21) Approximately 70% of all newly diagnosed cancer cases are captured annually. This study was exempt from institutional IRB review.

Variables

Demographic characteristics of interest included age, gender, race, comorbidities (Charlson Comorbidity Index > 0), insurance status (uninsured, private or government), cancer center type (academic versus non-academic), education level (percent of population within patient zip code without high school education ≥ 21% or <21%), year of diagnosis, region (grouped into 4 geographic areas, including: Northeast, Midwest, South and West), distance traveled to facility (miles), location (population ≥ 250,000 vs <250,000) and year of diagnosis (2004–2007, 2008–2011, 2012–2015). Histopathologic data included tumor location (lower third/cardia NOS/abdominal, Middle Third/Thoracic, Upper Third/Cervical, Overlapping, Esophagus NOS), histology (adenocarcinoma, squamous cell carcinoma or carcinoma NOS), and differentiation grade (well/moderate, poor/undifferentiated or unknown). Treatment was defined as having received any recommended therapy for esophageal cancer, including chemotherapy, radiation, surgery, or any combination of these interventions. As previously described elsewhere, treatments were categorized into surgery, definitive chemoradiation, induction + surgery (surgery and neoadjuvant chemotherapy ± radiation and/or adjuvant chemotherapy ± radiation), palliative (chemotherapy or radiation alone), and no treatment.[26] (Appendix 1) For patients that underwent surgery, postoperative 30-day mortality and readmission rate was recorded.

The American Joint Committee on Cancer (AJCC) staging criteria are recorded in concordance with diagnosis year. To account for different categorization of staging between the 6th and 7th AJCC editions, stage was divided into three categories using clinical data, including: local, locoregional, and metastatic, as previously described by Wong et al.[27, 28] (Appendix 2)

Statistical Analysis

Patients were divided into 4 groups based on age quartiles. Baseline patient demographics and clinical factors were compared between age groups using chi-square for categorical variables and Wilcoxon rank sum test for continuous variables. Data was reported as counts (percentages) and medians (interquartile range), respectively. Overall survival was defined as time (in months) from diagnosis to death or last follow-up. Survival analysis was performed using the Kaplan-Meier method. A multivariate model using Cox regression analysis was included to determine whether age independently impacted survival after adjusting for treatment and stage. A sub-analysis was performed among patients <50 and ≥ 50 as well as <60 and ≥ 60 as well as, to reflect the guidelines discussed in Table 1.

Given the large sample size of this study (>100,000), all comparisons between groups were statistically significant to $p<0.0001$. As such, the p values should be interpreted with caution as statistical significance may not always correspond with clinical significance. All data

analyses were performed using SAS v9.4 (SAS Institute, Carey, North Carolina) and R v3.3.3.

RESULTS

There were 101,596 patients included in the study cohort. The median age was 65 (57–74). Patients were grouped by quartiles of age distribution, which included: 1) 18–57 years (n=26,440) 2) 58–65 (n=25,162) 3) 66–74 (n=26,135) and 4) 75+ (n=23,589). The median and IQR by age group was 52 (IQR 47–55), 62 (IQR 60–64), 70 (IQR 67–72), and 80 (IQR 77–84). In this population 34.7% of patients were under age 60.

Clinicopathologic Characteristics

Comparison of baseline demographics between age groups is given in Table 2. The youngest age quartile had the highest rate of non-white patients compared to other age groups. Gender was similar amongst the younger three age quartiles (13.5%, 13.1%, and 15.7% respectively); however, there were 24.7% females in the 75 and older group. Patients in the youngest quartile were more likely to be uninsured and live in less educated areas than other age groups. With increasing age, distance from the hospital and rate of treatment at an academic center decreased. Patients had similar tumor location and grade.

Staging

Distribution of tumor stage by age group is presented in Figure 1. Patients aged 18–57 had the lowest rate of local disease (37.3%), with incidence rising with increasing age group (41.4%, 46.5% and 55.6%, respectively). Rates of locoregional disease were similar between the youngest three agree groups, and lowest in the oldest patients. Distant disease at diagnosis decreased with increasing age; 33.9% of patients age 18–57 had metastasis, followed by 29.8%, 26.8% and 23.1% in the respective increasing age groups. The rate of advanced disease at diagnosis, including locoregional and distant, was highest in the youngest age group (62.5%) and lowest in the patients aged 75+ (44.4%).

Treatment

Disease treatment by age quartile is demonstrated in Table 3. Non-treatment was twice as likely in patients age 75+ (32%) compared to patients in other age groups (14%, 15% and 17%, respectively by increasing age quartile). The rate of patients receiving definitive chemoradiation and surgery alone were similar between all groups. Patients in the youngest two age quartiles underwent induction + surgery more frequently (22.3% and 21.7% respectively) than patients in the third and fourth quartiles (17.3% and 5.2%, respectively).

Among patients that underwent surgical treatment, patients aged 75+ received local endoscopic therapy most frequently and were least likely to receive esophagectomy. On operative pathology, nodal metastasis rates were similar between age groups; however, the incidence of advanced T stage decreased with increasing age group. Postoperative readmission rates were similar among all groups, but 30-day overall mortality rates increased with age (0.7%, 0.9%, 1.4% and 1.3%, respectively).

Survival

Comparison of overall survival by age quartile is presented in Figure 2. Median OS was similar in patients age 18–74 (16.5–18.3 months), and much lower in patients with age 75+ (9.6). Stratification of overall survival by age quartile and tumor stage is shown in Figure 3. In patients with local disease, median OS in patients age 18–57 and 58–65 was similar (38.4 and 38.7 months); however, for age 66–74 and 75+ OS decreased (31.2 months and 13.0, respectively). The differences between age groups were less apparent for patients with locoregional disease (23.5, 22.6, 18.4 and 11.9, respectively by increasing age quartile). Among patients with metastatic disease, median OS ranged from 4–8 months. 5-year overall survival by age and stage is presented in Supplemental Table 1.

In Figure 4, median OS by age quartile was stratified by treatment selection. Among patients that underwent definitive chemoradiation, no difference in median OS was observed by age group (12.8–13.6 months). Similarly, minimal difference was observed among patients that underwent palliative treatment or received no treatment. However, among patients that underwent induction + surgery, median OS was much lower in patients in the oldest quartile (24.3 months) compared to younger groups (37.7, 37.3 and 33.4, respectively from quartile 1–3). Similarly, among patients that underwent surgical resection alone, patients age 75+ had lower median OS (30.1 months) compared to other groups (75.4, 81.9 and 55.3 months, respectively from quartile 1–3). Table 4 presents the results of multivariate cox proportional hazards assessing survival. After adjusting for stage and treatment, mortality risk increased with age quartile as compared to the youngest patients.

Dichotomized Analysis

In order to account for the age cut-offs described in the guidelines in Table 1, separate analyses were conducted by dividing the population using the age cutoff of 50 and 60. (Supplemental Table 2 and 3) Stratification by age 50 demonstrated several differences from the quartile analysis. The racial difference between older and younger patients was greater, with the group <50 having a 68% higher rate of non-white patients than > 50. Patients <50 had a 31% higher rate of distant disease at diagnosis (36.6% vs 27.8%) and those <60 had a 28% higher rate (33.6% vs 26.2%). (Figure 5a and b) There was less variation in overall survival by stage and treatment between age groups as compared to the quartile analysis. (Supplemental Figure 1 and 2)

DISCUSSION

The presentation and outcomes of esophageal cancer in young patients is poorly understood. Our study is the largest to date to compare characteristics of esophageal cancer by age. The majority of available studies have been small and demonstrated conflicting results.[9–12, 14–20] Furthermore, comparability is limited by varying definitions of “young”. As such, we utilized quartiles of age distribution (18–57, 58–65, 66–74, 75+) in this study to determine how young patients may differ compared to other age groups, but performed sub-analyses using age 50 and 60 as a cutoff to reflect current guideline cutoffs. (Table 1). Given that the incidence of esophageal cancer, a highly morbid disease, is rising among younger patients, there is an important need for consensus regarding the impact of age on the presentation and

outcomes of esophageal cancer.[7,8] Our findings support previous studies that demonstrated advanced disease presentation in younger patients.[14, 15, 17–19] Furthermore, results of our analysis demonstrated that the incidence of metastatic disease at diagnosis decreased with increasing age quartile. Use of age 50 and 60 as a cutoff demonstrated that the rate of distant disease was around 30% higher for younger patients in both analyses. In the only other population-based study, Zeng et al recently used Surveillance, Epidemiology, and End Results (SEER) program data to evaluate 1385 patients age ≤ 50 and demonstrated that 48.5% presented with distant disease compared to 37.9%of older patients.[18] The higher rate of patients with metastatic disease may reflect selection bias in the authors' methodology, including the decision to not analyze patients with esophagogastric junction cancer and use of AJCC 6th edition for staging. However, their results confirm our conclusion that younger age is associated with more advanced disease and that this represents an important area for intervention.

This study demonstrated similar tumor grade between groups, suggesting that observed differences in stage are not a reflection of a more aggressive disease process but rather delayed diagnosis. In support of this observation, several studies noted a longer period of reported symptoms and slower referral to endoscopy among young patients.[14, 15] The high rate of adenocarcinoma in the youngest age quartile is consistent with the demonstrated rising incidence of adenocarcinoma in the United States.[12, 13] Currently, gastroesophageal reflux disease is the only well accepted risk factor for development of esophageal adenocarcinoma. Recent data has reported that up to 40% of people in the United States report symptoms of gastroesophageal reflux.[29] It has previously been described that the time for progression from reflux to Barrett's esophagus is approximately 10 years.[30, 31] As such the decision to perform endoscopic evaluation in a symptomatic patient should focus on length of time they have had gastroesophageal reflux disease rather than age. People with known gastroesophageal reflux disease as children or adolescents should be considered at risk. As the rates of premature birth, childhood obesity and high consumption of high fat foods in the United States continue to increase, it is possible that increasing rates of esophageal adenocarcinoma may be observed in the young.[32–34] Recent data from the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) assessing age-specific risk profiles demonstrated that the associations between reflux disease and obesity were stronger among those who developed cancer at a younger age.[35] Our findings support the warning by Hamouda et al against over reliance on age cutoffs and alarm symptoms based on previous studies that have questioned the efficacy of these factors as underlying predictors of cancer.[23,36] Instead, clinicians should focus on the patient as a whole. Age quartile analysis demonstrated minimal differences in the demographic "profile" of patients <75 years old. However, evaluation using age 50 as a cutoff demonstrated that patients < 50 years old had a significantly higher rate of non-white race and were more likely to be uninsured as compared to older patients This is important given the guidelines in Table 1 mention White race as a risk factor. Previous studies have demonstrated racial disparities in stage at diagnosis, treatment selection and prognosis among non-White patients, which may in part reflect differences in socioeconomic status.[26, 37–39] Further research may investigate whether there are underlying genetic factors that may contribute to earlier development of esophageal cancer in certain patients. However, the absence of distinguishing findings

support the conclusion that physicians must maintain a high clinical suspicion in patients with prolonged histories of reflux symptoms, and recognize that not all patients present in the “typical” fashion (elderly white males).

Previous studies have suggested that more aggressive treatment selection among young patients results in similar overall survival despite more advanced stage at diagnosis.[14, 15, 17, 23] While some studies demonstrate improved 5-year overall survival among younger patients, others fail to replicate these findings.[14–19, 23] In this series, patients < 75 had a similar rate of any surgical therapy, although patients < 65 were more likely to get aggressive treatment with induction therapy + surgerythan older patients.. However, stratification by stage demonstrated that the magnitude of survival benefits among younger patients decreased with increasing stage. This highlights the importance of early diagnosis for esophageal cancer, especially in younger patients who have less comorbidities and can better tolerate aggressive curative therapy. Once distant disease is diagnosed, overall prognosis is very poor regardless of age.

Interpretation of our results are subject to the limitations associated with utilization of NCDB data. It is not possible to determine whether young patients in this series had a delay in diagnosis because of lower clinical suspicion as it relates to patient age. However, this hypothesis is supported by current understanding of perceptions of esophageal cancer amongst providers, endoscopic screening guidelines, smaller studies that did identify delayed presentation in younger patients, and the absence of markers of more aggressive tumor pathology as an underlying etiology for advanced stage at diagnosis. Additionally, NCDB does not provide information regarding postoperative complications or toxicity because of chemotherapy or radiation. As such, it is difficult to determine why a survival difference was observed between age groups among patients undergoing surgical treatments. Furthermore, the specific chemotherapy agents given are not included, and therefore it is not possible to determine whether patients that underwent treatment at non-academic centers received the most updated standard of treatment. Finally, it is not possible to assess the impact of birth cohort on observed differences between age groups with this dataset. However, the increasing incidence of esophageal adenocarcinoma has still been demonstrated in more recent birth cohorts.[13]

CONCLUSIONS

The results of this demonstrate that in a large cohort compromising the majority of cases of esophageal cancer in the United States between 2004 to 2015, young patients with esophageal adenocarcinoma had more advanced disease at diagnosis despite similar clinicopathologic tumor characteristics. Given that stage at diagnosis is the most important determinant of overall survival for this highly lethal disease, it is important that clinicians consider esophageal cancer in the differential diagnosis of symptomatic patients with high-risk histories,, such as obesity and prolonged reflux. Patient symptoms and risk factors, rather than age alone, should be considered when deciding whether to perform endoscopic evaluation. Esophageal cancer is not only a disease of older patients. (Figure 5)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

Appendix 1. Definition of treatment groups

SURGERY	
	Surgery in first 180 days from Dx
	No radiation or chemo within first 180 days
	Surgery in first 180 days from Dx
	Radiation and/or chemo in first 180 days
	Number of days to surgery < days to chemo/rad
PALLIATIVE CARE	
	Chemo in first 180 days from Dx
Chemo Only	No radiation within first 180 days
	No surgery within first 180 days
	Radiation in first 180 days from Dx
Rads Group B	No chemo within first 180 days
	No surgery within first 180 days
DEFINITIVE CHEMORADIATION	
	Chemo within first 180 days from Dx
Subsequent	Radiation within first 365 days
	Days between start of chemo and start of radiation is >7
	Chemo within first 180 days from Dx
Concurrent	Radiation within first 365 days
	Days between start of chemo and start of radiation is <7
INDUCTION + SURGERY	
	Chemo in first 180 days
	Surgery in first 180 days
Chemo alone + surgery	Number of days to chemo < number of days to surgery
	Chemo starts more than 7 days before surgery
	Chemo and radiation in first 180 days
	Surgery in first 180 days
Chemo + radiation concurrent + surgery	Number of days to chemo/rad < number of days to surgery
	Number of days between start of chemo and start of rad is < 7

	Chemo and/or radiation in first 180 days from Dx
Other Induction + surgery (radiation alone or chemorad subsequent)	Surgery in first 180 days
	Number of days to chemo/rad < number of days to surgery
	Number of days between start of chemo and start of rad is > 7
	Radiation in first 180 days from Dx
Radiation Group A	No chemo within first 180 days
	Radiation occurs before any surgery (surg would be salvage)
NO TREATMENT	
No Treatment	No treatment within 180 days

Appendix 2.: Staging

Stage	Definition
Local	Unknown or a tumor of any size, unknown or no nodes, and unknown or no metastatic disease (Tx-4, Nx-0, Mx-0)
Locoregional	Unknown or a tumor of any size, positive nodes, and unknown or no metastatic disease (Tx-4, N1–3, Mx-1A)
Distant	Unknown or a tumor of any size, unknown nodes or positive nodes, and having a metastatic diagnosis (Tx-4, Nx-3, M1-M1B)

Adapted from Wong et al[28]

GLOSSARY OF ABBREVIATIONS

OS	Overall Survival
DFS	Disease Free Survival
DSS	Disease Specific Survival
EAC	Esophageal Adenocarcinoma

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CENTRAL MESSAGE

Perceptions of esophageal cancer as a disease of the elderly may result in the higher rate of advanced diagnostic stage in younger patients. Risk factors, rather than age, should guide evaluation.

PERSPECTIVE STATEMENT

This population-based study showed similar clinicopathologic characteristics but more advanced disease among young patients diagnosed with esophageal adenocarcinoma.. Given poor prognosis associated with metastatic esophageal cancer, itmay be time to rethink the approach for evaluation of young high-risk patients.

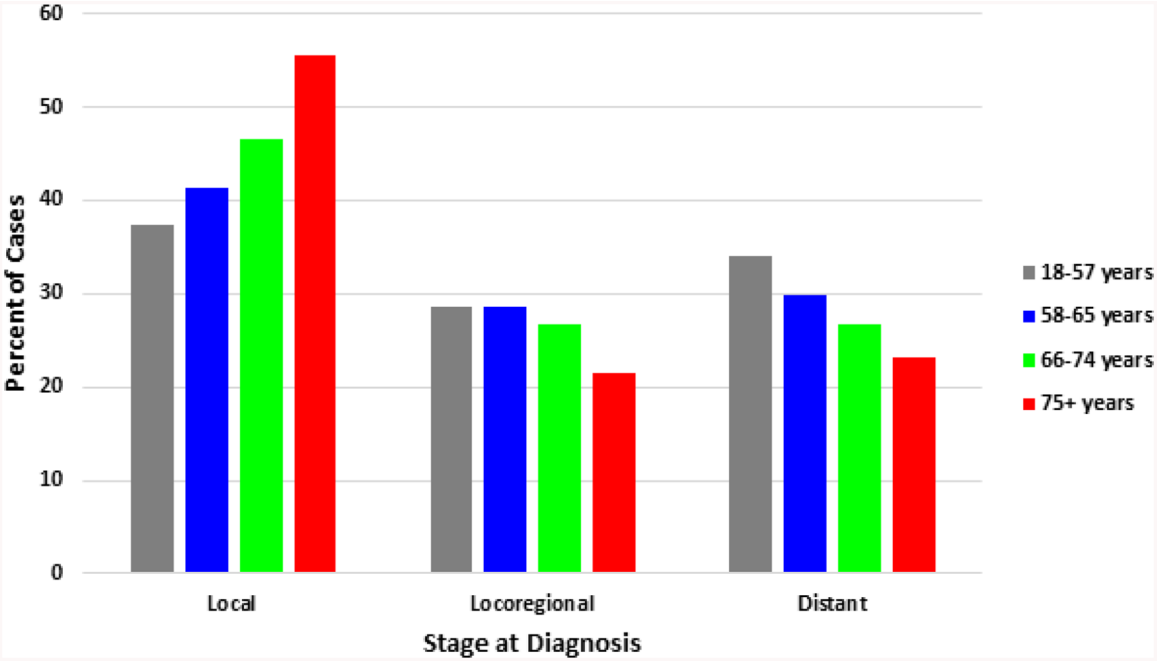


Figure 1.
Distribution of stage at diagnosis by age quartile at diagnosis

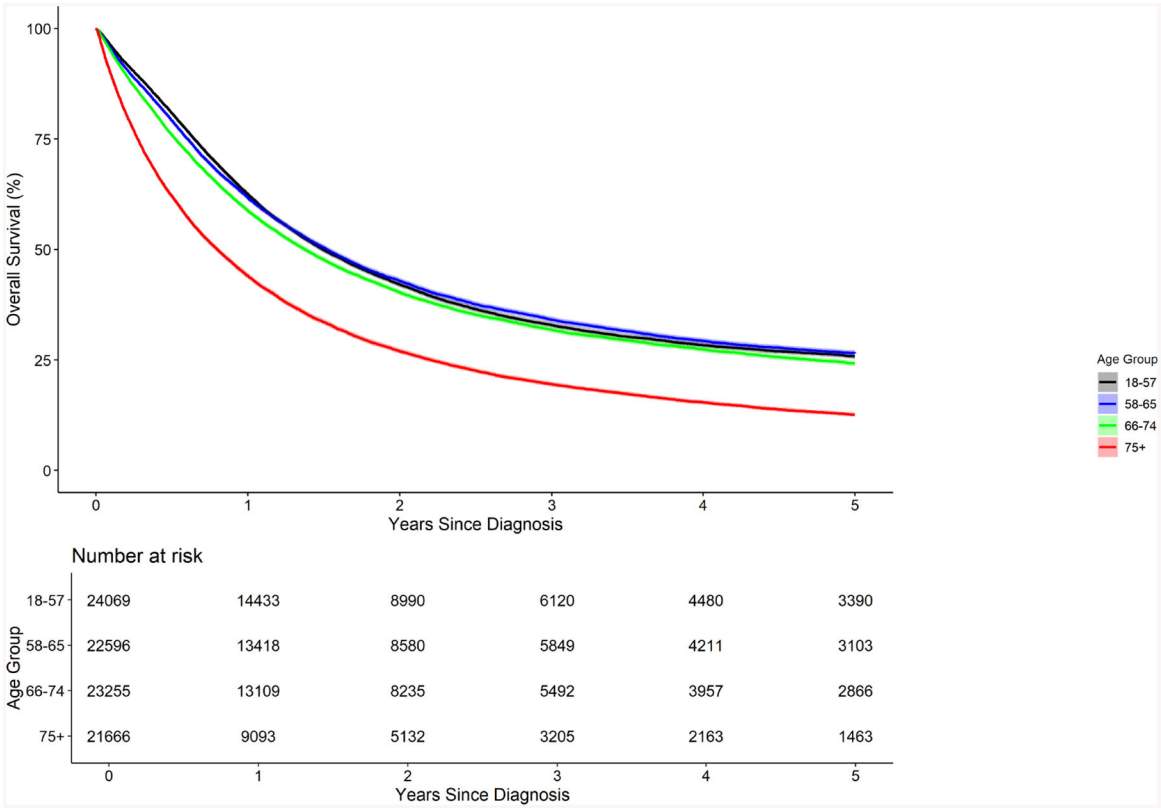


Figure 2.
Comparison of overall survival by age quartile

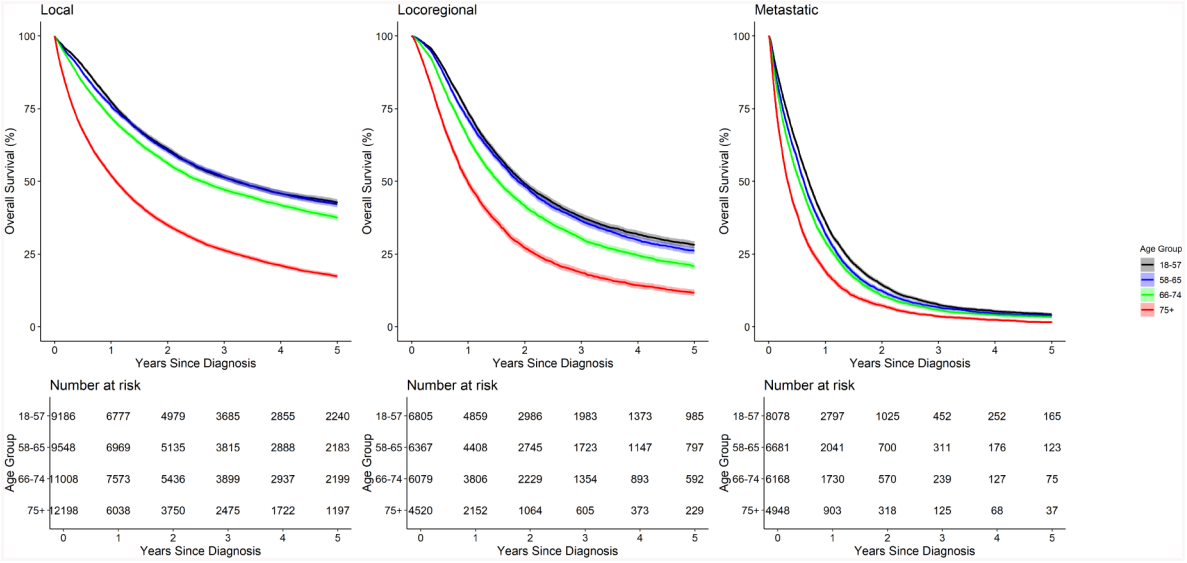


Figure 3.
Comparison of overall survival by age quartile, stratified by tumor stage at diagnosis

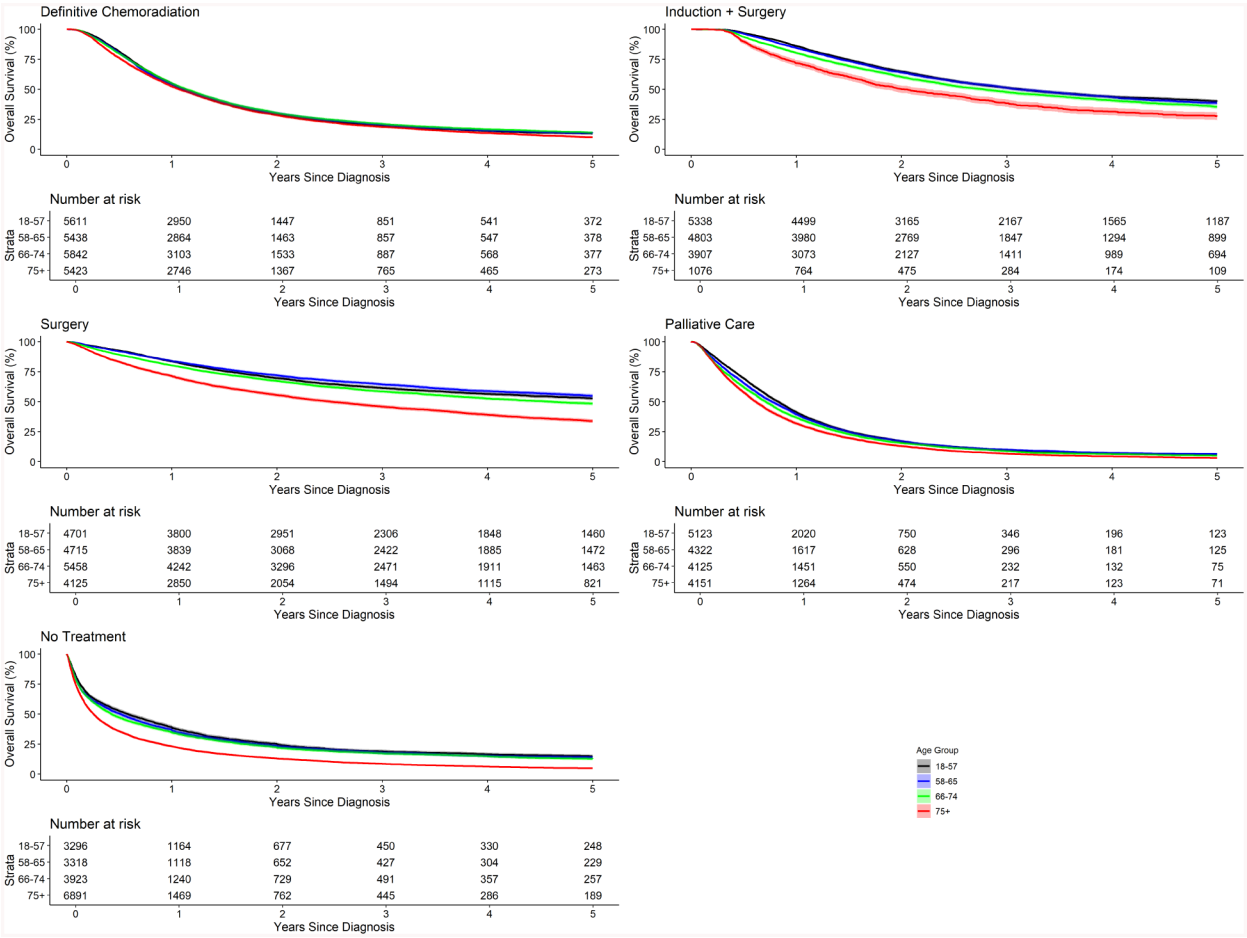
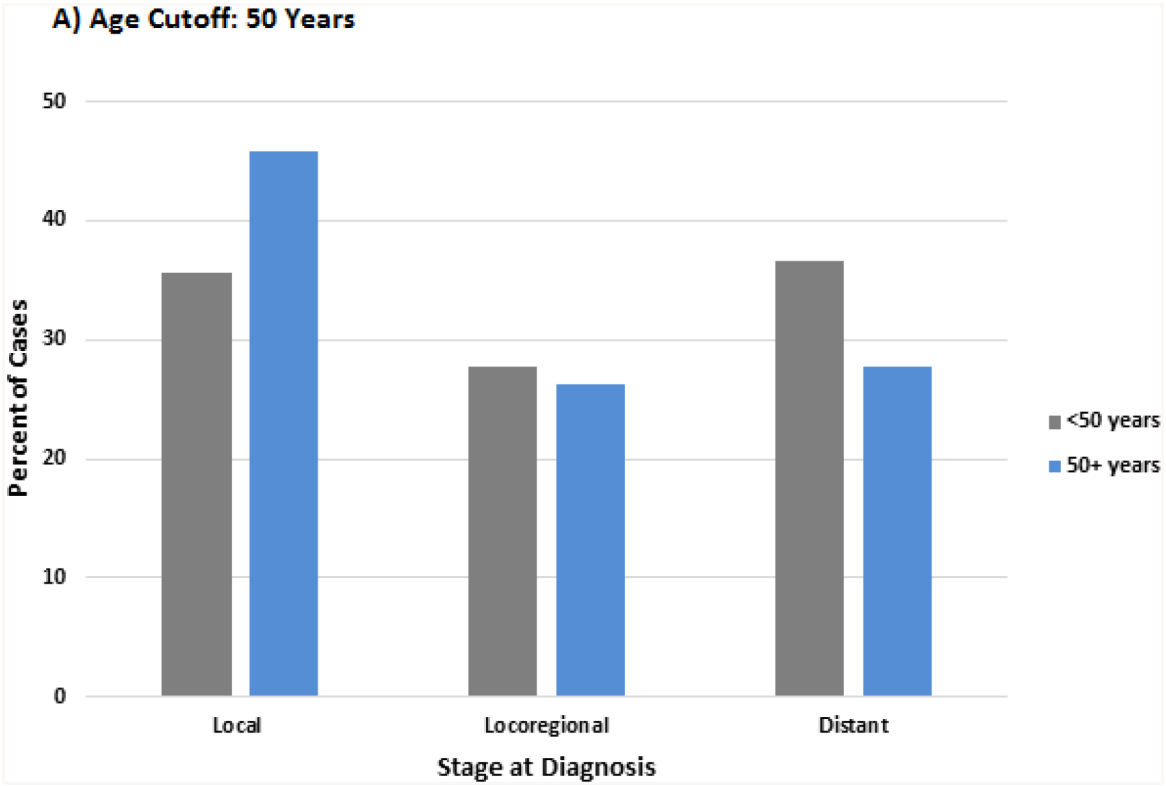


Figure 4.
Comparison of overall survival by age quartile, stratified by treatment selection



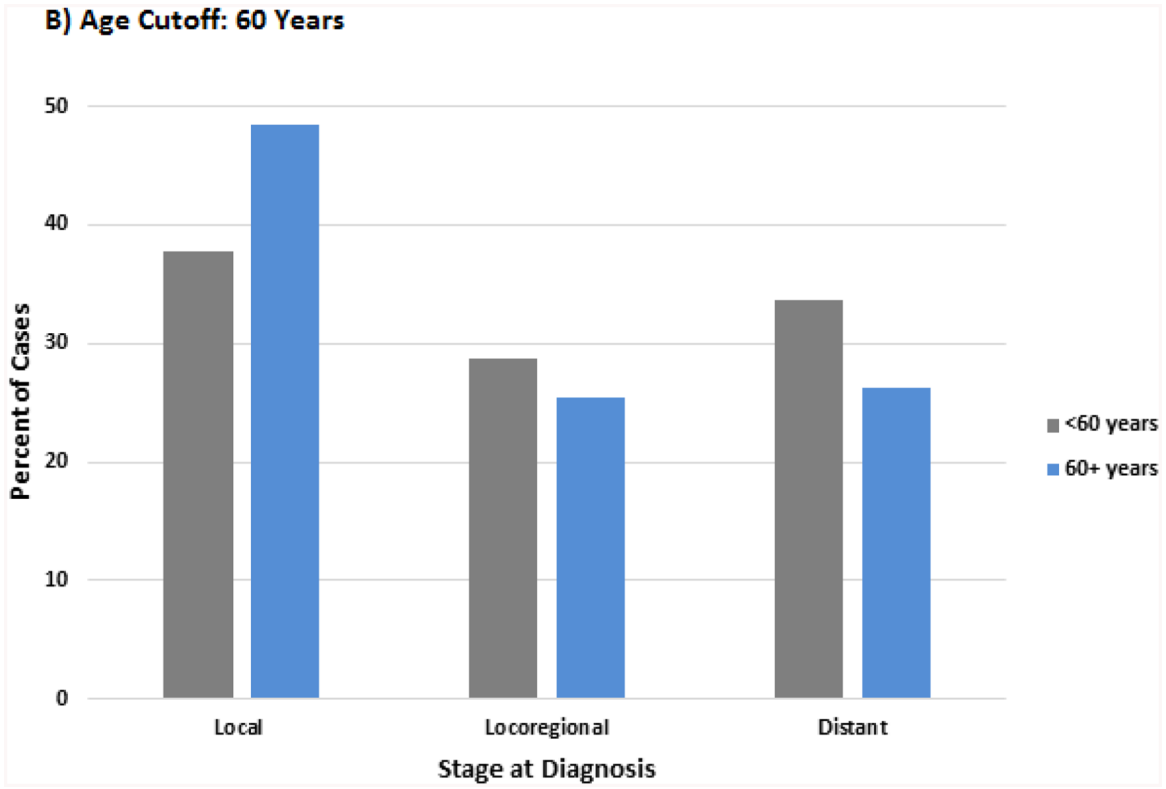


Figure 5A,B.

Distribution of stage at diagnosis by age cutoff A) 50 years B) 60 years

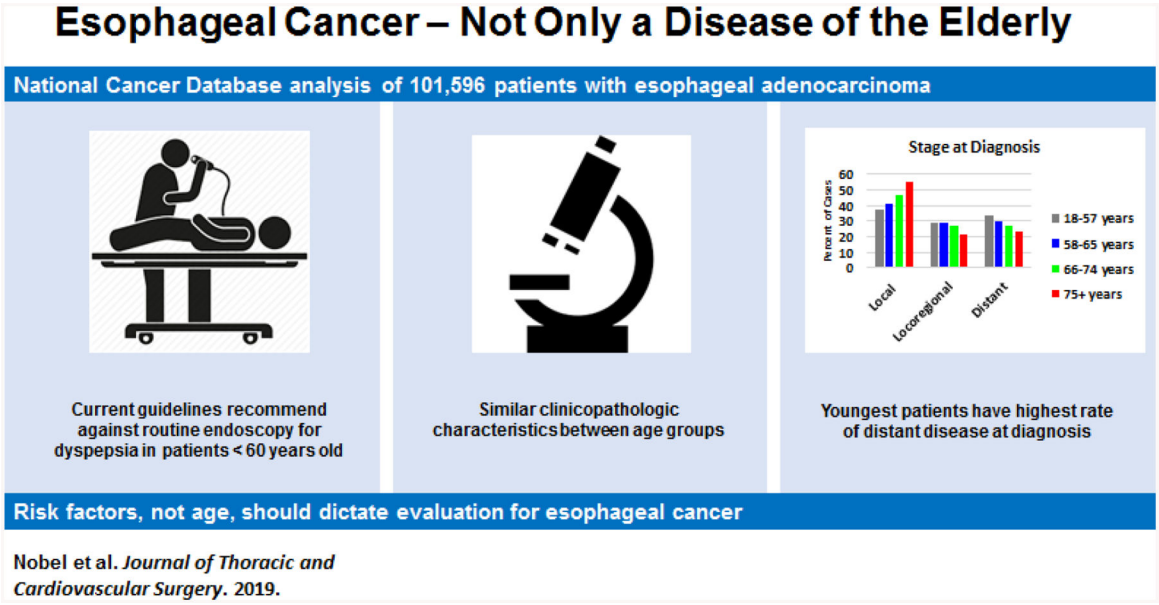


Figure 6.

Graphical Abstract. Esophageal cancer diagnosed at median age of 68 and is considered a disease of the elderly. In this large series of patients with esophageal cancer from the National Cancer Database (2004–2015), although clinicopathologic similarities suggest similar tumor biology between age groups, the youngest age quartile had the highest rate of distant disease at diagnosis (34% versus 29.9, 26.8 and 23.1%, respectively with increasing age group). Risk factors, such as obesity and prolonged history of reflux, should dictate evaluation of esophageal cancer rather than age.

Table 1.

Current guidelines for endoscopic evaluation of gastroesophageal reflux disease and Barrett's Esophagus (BE)

	Indications for Endoscopic Evaluation	High Risk Features
American Society of Gastrointestinal Endoscopy (2015)[5]	Screening EGD for select patients with prolonged history of GERD	Age ≥ 50, chronic GERD symptoms (>5 years), white, male, nocturnal reflux
American Gastroenterological Association (AGA) (2008, 2011)[6, 7]	Consider EGD to screen for BE in patients with high risk	Age ≥50, male, white, hiatal hernia, elevated BMI, intra-abdominal fat distribution
American College of Gastroenterology (ACG) (2016)[8]	Consider screening for BE in high risk patients	Chronic GERD symptoms (>5 years) and 2+ BE/cancer risk factors: age ≥ 50, white, central obesity, current/past history of smoking, family history
American College of Gastroenterology (ACG) (2013)[9]	Individualized EGD for GERD diagnosis in select patients for alarm symptoms and high risk	Elderly, those at risk for BE, noncardiac chest pain, patients unresponsive to PPI
AGA and ACG (2017)[4]	EGD should be performed in patients age> 60 with dyspepsia to rule out neoplasia	NA

EGD: esophagogastroduodenoscopy; GERD: gastroesophageal reflux disease; BE: Barrett's Esophagus; NA: not applicable.

Table 2.

Comparison of Demographic Characteristics by Age Group

Characteristic, N (%)	Age Quartile Groups				
	18–57	**58–65**	**66–74**	**75 +**	**p overall**
N	26440	25162	26135	23859	
Female Gender	3567 (13.5%)	3289 (13.1%)	4101 (15.7%)	5903 (24.7%)	<0.001
White Race	23197 (87.7%)	22855 (90.8%)	23989 (91.8%)	21850 (91.6%)	<0.001
Any Comorbidities	5215 (19.7%)	6921 (27.5%)	8403 (32.2%)	7672 (32.2%)	<0.001
Median Distance to Hospital, miles (IQR)	13.4 [1.50; 143]	13.4 [1.50; 148]	12.8 [1.40; 146]	8.80 [1.10; 104]	<0.001
Education (≥21% in zip code without high school diploma)	4117 (15.6%)	3507 (13.9%)	3513 (13.4%)	2769 (11.6%)	<0.001
Insurance Status					<0.001
Government	6145 (23.2%)	8202 (32.6%)	21526 (82.4%)	21021 (88.1%)	
Private	17630 (66.7%)	15183 (60.3%)	3806 (14.6%)	2246 (9.41%)	
None	1774 (6.71%)	1027 (4.08%)	170 (0.65%)	117 (0.49%)	
Insurance Status Unknown	891 (3.37%)	750 (2.98%)	633 (2.42%)	475 (1.99%)	
Facility Type					<0.001
Academic	10964 (44.3%)	10926 (43.4%)	10656 (40.8%)	8173 (34.3%)	
Non-Academic	13784 (55.7%)	14236 (56.6%)	15479 (59.2%)	15686 (65.7%)	
Location					<0.001
East	5428 (21.9%)	5703 (22.7%)	6021 (23.0%)	5999 (25.1%)	
South	7211 (29.1%)	7233 (28.7%)	7306 (28.0%)	7000 (29.3%)	
Midwest	8551 (34.6%)	8406 (33.4%)	8639 (33.1%)	6967 (29.2%)	
West	3558 (14.4%)	3820 (15.2%)	4169 (16.0%)	3893 (16.3%)	
Patient Location (Combine into ≥250,000)	20717 (78.4%)	19603 (77.9%)	20252 (77.5%)	19085 (80.0%)	<0.001
Diagnosis Year					<0.001
2004–2007	8194	6844	7124	7411	

Characteristic, N (%)	Age Quartile Groups				
	18–57	58–65	66–74	75 +	p overall
	(31.0%)	(27.2%)	(27.3%)	(31.1%)	
2008–2011	8867	8377	8404	7836	
	(33.5%)	(33.3%)	(32.2%)	(32.8%)	
2012–2015	9379	9941	10607	8612	
	(35.5%)	(39.5%)	(40.6%)	(36.1%)	
Tumor Site					<0.001
Abdominal/Lower/Stomach	22715	21614	22647	20089	
	(85.9%)	(85.9%)	(86.7%)	(84.2%)	
Overlapping	740	751	667	611	
	(2.80%)	(2.98%)	(2.55%)	(2.56%)	
Thoracic/Middle	962	966	1011	1219	
	(3.64%)	(3.84%)	(3.87%)	(5.11%)	
Unspecified	1837	1663	1654	1727	
	(6.95%)	(6.61%)	(6.33%)	(7.24%)	
Upper/Cervical	186	168	156	213	
	(0.70%)	(0.67%)	(0.60%)	(0.89%)	
Differentiation Grade					<0.001
Unknown	4801	4585	4925	4883	
	(18.2%)	(18.2%)	(18.8%)	(20.5%)	
Well/Moderate	9930	9639	10112	9140	
	(37.6%)	(38.3%)	(38.7%)	(38.3%)	
Poor/Undifferentiated	11709	10938	11098	9836	
	(44.3%)	(43.5%)	(42.5%)	(41.2%)	

Table 3.

Comparison of Treatment Selection Between Age Groups

Treatment Type	Age Quartile Groups			
	18–57	**58–65**	**66–74**	**75 +**
Definitive Chemoradiation	6211 (23.5%)	6062 (24.1%)	6641 (25.4%)	6038 (25.3%)
Induction + Surgery	5907 (22.3%)	5466 (21.7%)	4521 (17.3%)	1249 (5.23%)
Surgery	5056 (19.1%)	5108 (20.3%)	5984 (22.9%)	4459 (18.7%)
Palliative Care	5698 (21.6%)	4850 (19.3%)	4649 (17.8%)	4592 (19.2%)
No Treatment	3568 (13.5%)	3676 (14.6%)	4340 (16.6%)	7521 (31.5%)

Table 4.

Adjusted model for overall survival

	HR	95% CI	*p* value
Age quartile			
18–57	Ref		
58–65	1.05	1.03, 1.07	<.001
66–74	1.15	1.13, 1.18	<.001
75 +	1.62	1.58, 1.65	<.001
Treatment			
Definitive chemoradiation	Ref		
Induction + surgery	0.57	0.55, 0.5S	<.001
No treatment	1.79	1.75, 1.83	<.001
Palliative care	1.18	1.15, 1.20	<.001
Surgery	0.48	0.47, 0.50	<.001
Stage			
Local	Ref		
Locoregional	1.27	1.24, 1.30	<.001
Metastatic	2.53	2.48, 2.58	<.001

HR, Hazard ratio; *CI*, confidence interval