Esophageal cancer in young patients: does age affect treatment course and outcomes?

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Background: Young patients with esophageal cancer (EC) are believed to have more aggressive disease, thus thought to have worse survival. Herein, we aim to study the impact of younger age on the short- and long-term outcomes of esophagectomy for EC.

Methods: Patients who underwent esophagectomy for EC at our institution between 1994–2019 were included. Age 50 was defined as the cutoff for "young" *vs.* "old". Patients from each age group were propensity-score matched 1:1 to compare postoperative and survival outcomes.

Results: Our database reported 1,031 patients, 112 of whom were in the 'young' group. For the unmatched analysis, young patients were more likely to have squamous cell carcinoma, higher rates of locally advanced disease, and subsequently higher rates of neoadjuvant chemotherapy (79.5% *vs.* 68.3%; P=0.047). After matching for pre-treatment clinical factors, young patients were less likely to have pulmonary or cardiac complications after surgery, and three times more likely to receive AC despite matching for stage and response to treatment (26.7% *vs.* 7.9%; P=0.002). Then, we matched patients including receipt of AC to study survival. In the second match, median recurrence-free survival (RFS) for young patients was 49.0±26.0 *vs.* old 27.0±5.4 months (P=0.215). Median overall survival (OS) for young was 73.0±28.9 *vs.* old 31.0±6.3 months (P=0.073).

Conclusions: Young EC patients tend to present with more advanced disease. However, when matched for stage and response to therapies, young patients were three-times more likely to be offered AC. After adjusting for receipt of adjuvant therapy no difference was detected in RFS.

Keywords: Esophageal cancer (EC); adjuvant therapy; young patients

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Introduction

The incidence of esophageal cancer (EC) has been rising rapidly over the past 40 years (1-7). While EC is typically diagnosed in older patients in their sixth and seventh decades of life, there has been an evident uptrend within younger patients (2,6,7). This growth is particularly concerning as the prognosis for EC is poor, with 3- and 5-year survival rates ranging from 6–50% and 17–39%, respectively (1,8-13).

Within the literature, the common belief is that younger patients diagnosed with EC present at a later stage of the disease (2,3,7). A study by Boys *et al*. identified that patients under 40 were more likely to present at a later stage than those over 40 years and had a shorter median overall survival (OS) (2). It is also hypothesized that these patients may experience longer delays from their onset of symptoms to work-up of their cancer than older counterparts. Additionally, it has also been reported than younger patient may have tumors that exhibit a more aggressive biology, all factors that call for more effective treatment options for the younger population.

Currently, the standard of care for locally advanced EC, as delineated by the CROSS trial, is neoadjuvant chemoradiation followed by surgical resection, which demonstrated a clear survival benefit over surgical resection alone (14). However, there is an active debate on whether age plays a role in treatment selection and outcomes. Our group, among others, has reported that chronologic age may not entirely be a contraindication to esophagectomy, as octogenarians have been shown to tolerate surgery (15-17). As the body of literature expands for the older population, clinical characteristics and outcomes for EC in the young have not been well described. In this study, we seek to compare stage at diagnosis, treatment modalities and outcomes for patients ≤50 *vs*. >50 years of age diagnosed with EC.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/aoe-20-92).

Methods

All patients diagnosed with EC and treated with an Ivor-Lewis esophagectomy between 1994 and 2019 at our institution were included in the database. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of H. Lee Moffitt Cancer Center (*MCC15030*) and individual consent for this retrospective analysis was waived. Demographics, perioperative, and long-term follow up data were collected under an IRB-approved institutional protocol. Patients with other histologic diagnosis aside from squamous cell carcinoma and adenocarcinoma were not included in this analysis.

The appropriate age cutoff for determination of 'young' versus 'old' in cancer epidemiology is an area of ongoing debate. Although studies have used the cutoff of <40 years as a reference for adolescents and young adults (AYA) in line with the SEER reporting (2), there are several other studies have set the precedent of utilizing 50 years as an age cutoff based on the distribution of the patients' age groups (18,19). Furthermore, current American Cancer Society epidemiology reports indicate a <10-fold probability of EC occurrence and mortality inpatients <50 years of age (20). In line with our institutional practice of recommending genetic testing for patients with a new diagnosis of EC, we believe that the age cutoff of 50 years would reasonably differentiate genetic origin or biologic behavior of disease. As such, for purposes of our analysis, we used age 50 as the set limit between 'young' (≤50) and 'old' (>50) to establish two comparative age groups.

Our institutional protocol involved early adoption of delivering neoadjuvant therapy (NAT) for patients with locally advanced gastroesophageal cancers beginning in 1994. Specifically, over the course of this study, NAT was given to patients with T2 or nodal positive disease as defined by CT, PET, or endoscopic ultrasound that was performed starting in 1994 and becoming more routine for all patients starting in 2000.

Postoperative complications defined in our study are in concordance with the basic platform of complications defined by the esophageal complications consensus group (ECCG) guidelines (21). In addition, failure to thrive was included as a complication, which is defined by the United States National Institute of Aging as a syndrome of global decline characterized by weight loss, inactivity, decreased appetite and poor nutrition, often accompanied by dehydration, depressive symptoms, impaired immune function, and low cholesterol (22).

The first aim was to compare the outcomes of young and old patients when matching for clinical characteristics and treatment modalities. Therefore, a propensity score was calculated based on a multivariate regression model including all the variables that could influence the decision on adjuvant chemotherapy (AC) except for the patients'

age group. Patients from each group were matched 1:1 using the nearest neighbor method with a caliper width of 0.1 standard deviations with a conditional exact matching for clinical stage. Conditional logistic regression was applied to compare categorical variables between the groups, and mixed effect modeling was used for continuous variables. A logistic regression analysis was also conducted for overall complications.

The second aim was to compare long-term outcomes between young *vs.* old patients with respect to administration of AC. The match process was re-applied with the addition of AC into the regression model. Cox regression analysis was performed to confirm the influence of age on recurrence-free survival (RFS) and OS. Matching on a ratio of 1:1 was repeated in an identical fashion. Kaplan-Meier method was used to compare RFS and OS using the log-rank test. Of note, the 'event' in RFS was defined as evidence of recurrence or death. Statistical significance was set at <0.05 throughout the study. IBM SPSS v25 (Armonk, NY) with R Essentials plug-in (version 3.3.3) was used to perform data analysis.

Results

Our database included 1,031 patients with EC who were treated with Ivor-Lewis esophagectomy. Mean age was 63.8±28.0 and 86.5% were males. Mean BMI was 28.0±5.6. Nine-hundred thirty-nine patients (91.1%) had adenocarcinoma, whereas the remaining 92 (8.9%) had squamous cell carcinoma. Six-hundred seventeen patients (59.8%) had distal EC and 414 (40.2%) were classified as esophagogastric junction (EGJ) cancers. Six-hundred thirty-eight (61.9%) received neoadjuvant chemotherapy and 619 (60.0%) received neoadjuvant radiation with a median dose of 5,040 cGy. One third of the esophagectomies were performed using minimally-invasive techniques. Median hospitalization was 10 days, overall morbidity (all grades) was 65.5% and thirty-day mortality was 2.6%. *Table 1* summarizes the demographics and perioperative characteristics of our EC population treated with Ivor-Lewis esophagectomy.

One hundred and twelve patients fell in the young group and 919 in the old group. Upon comparison of the unmatched patients, there were statistically significant differences detected in histology, distribution of clinical stage, neoadjuvant treatment, and surgical approach. Young patients were more likely to have squamous cell carcinoma than old patients (15.2% *vs.* 8.2%; P=0.014), higher rates of

locally advanced disease, and subsequently higher rates of neoadjuvant chemotherapy (79.5% *vs.* 68.3%; P=0.047). In addition, older patients were more likely to have minimally invasive Ivor-Lewis esophagectomy, likely as a reflection of their earlier stages at diagnosis. Presence of Barrett's esophagus was not statistically significant between young and old groups for both unmatched (41.4% *vs.* 44.4%, P=0.838) and matched (42% *vs.* 40%, P=0.335) patients. In the unmatched patients, there was no significant difference between the young and old groups for positive nodes (1.37±2.43 *vs.* 1.02±2.44, P=0.160), but there was a significant difference in ratio (0.14±0.25 *vs.* 0.08±0.19, P=0.010). However, after matching, the ratio became insignificant between young and old groups (0.11±0.21 *vs.* 0.12±0.23, P=0.752).

The first propensity score was calculated as described above to include all the clinical, pathological and survival variables except the patients' age group. One hundred and one patients were matched 1:1 from each group. The matched dataset demonstrated excellent balance as demonstrated by standard difference (SD) values <0.1 across all the variables and the significant differences resolved (P>0.05). *Table 2* demonstrates the comparative analysis of the unmatched and matched datasets.

Upon comparison of postoperative outcomes in the matched dataset, rates of overall morbidity did not differ between young and old patients in the matched dataset (63% *vs.* 65%; P=883). Young patients were shown to have lower rates of aspiration (0% *vs.* 6.9%; P=0.014), lower rates of cardiac arrhythmia other than atrial fibrillation (5.0% *vs.* 23.8%; P<0.001), and were three times more likely to be offered AC despite identical clinical staging and response to NAT (26.7% *vs.* 7.9%; P=0.002). However, old patients demonstrated higher rates of aspiration (6.9% *vs.* 0%; P=0.014) and cardiac arrhythmia (23.8% *vs.* 5%; P<0.001) which are considered severe. Mortality was also similar between the groups (3% *vs.* 3%; P=1.000). By accounting for all major complications combined (Clavien-Dindo III/IV), no difference was noted between the two groups. No differences were noted in other pulmonary or cardiac complications, anastomotic leak or stenosis, overall morbidity, or mortality.

Table 3 shows the comparison between the young and old patients in the matched dataset matched for adjuvant therapies. Young patients had higher rates of stage IV (7.1% *vs.* 1.6%), and somewhat comparable rates of other stage distribution. However, a definitive conclusion could not be drawn on the more advanced disease presentation within

Table 1 Comparison of young (≤50 years) *vs.* old (>50 years) patients treated with Ivor-Lewis esophagectomy in the unmatched and matched datasets

Variables	Unmatched dataset				Matched dataset 1:1			
	≤50 years	>50 years	SD	P	<50 years	≥50 years	SD	P
N	112	919			101	101		
Sex			0.045	0.151			0.053	0.452
Males	92 (82.1%)	800 (87.1%)			82 (81.2%)	86 (58.1%)		
Females	20 (17.9%)	119 (12.9%)			19 (18.8%)	15 (14.9%)		
Race			0.079	0.163			0.091	0.796
White	102 (91.1%)	882 (96.0%)			95 (94.1%)	96 (95.0%)		
Black	3 (2.7%)	7 (0.8%)			1 (1.0%)	2 (2.0%)		
Hispanic	4 (3.6%)	17 (1.8%)			2 (2.0%)	2 (2.0%)		
Asian	1 (0.9%)	4 (0.4%)			1 (.0%)	0 (0.0%)		
Other	2 (1.8%)	9 (1.0%)			2 (2.0%)	1 (1.0%)		
BMI	27.42±5.90	28.06±5.53	0.052	0.149	27.59±5.92	28.03±5.59	0.044	0.415
CCI			0.111	0.012			0.074	0.891
0	14 (12.5%)	48 (5.2%)			11 (10.9%)	11 (10.9%)		
1	19 (17.0%)	126 (13.7%)			16 (15.8%)	18 (17.8%)		
2	28 (25.0%)	212 (23.1%)			25 (24.8%)	30 (29.7%)		
3+	50 (44.6%)	528 (57.5%)			48 (47.5%)	41 (40.6%)		
Missing	1 (0.9%)	5 (0.5%)			1 (1.0%)	1 (1.0%)		
Smoking			0.073	0.063			0.044	0.819
No	41 (36.6%)	251 (27.3%)			36 (35.6%)	33 (32.7%)		
Yes	67 (59.8%)	648 (70.5%)			61 (60.4%)	65 (64.4%)		
Not reported	4 (3.6%)	20 (2.2%)			4 (4.0%)	3 (3.0%)		
Histology			0.076	0.014			0.014	0.841
Adenocarcinoma	95 (84.8%)	844 (91.8%)			86 (85.1%)	87 (86.1%)		
SCC	17 (15.2%)	75 (8.2%)			15 (14.9%)	14 (13.9%)		
Clinical stage			0.134	0.004			0.000	1.000
0	0 (0.0%)	16 (1.7%)			0 (0.0%)	0 (0.0%)		
I	10 (8.9%)	111 (12.1%)			10 (9.9%)	10 (9.9%)		
IIA	24 (21.4%)	173 (18.8%)			19 (18.8%)	19 (18.8%)		
IIB	10 (8.9%)	120 (13.1%)			10 (9.9%)	10 (9.9%)		
III	45 (40.2%)	335 (36.5%)			43 (42.6%)	43 (42.6%)		
IV	8 (7.1%)	15 (1.6%)			4 (4.0%)	4 (4.0%)		
Unstageable	15 (13.4%)	149 (16.2%)			15 (14.9%)	15 (14.9%)		

Table 1 (*continued*)

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Variables	Unmatched dataset				Matched dataset 1:1			
	≤50 years	>50 years	SD	P	<50 years	≥50 years	SD	P
Location			0.026	0.411			0.010	0.87
Distal esophagus	63 (56.3%)	554 (60.3%)			58 (57.4%)	57 (56.4%)		
EGJ	49 (43.8%)	365 (39.7%)			43 (42.6%)	44 (43.6%)		
Grade			0.082	0.071			0.050	0.300
Well diff.	7 (6.3%)	79 (8.6%)			7 (6.9%)	9 (8.9%)		
Moderately diff.	50 (44.6%)	319 (34.7%)			45 (44.6%)	38 (37.6%)		
Poorly diff.	50 (44.6%)	426 (46.4%)			44 (43.6%)	45 (44.6%)		
Not reported	5 (4.5%)	95 (10.3%)			5 (5.0%)	9 (8.9%)		
Neoadjuvant chemo	89 (79.5%)	627 (68.3%)	0.077	0.047	71 (70.3%)	70 (69.3%)	0.039	0.855
Neoadjuvant XRT	77 (68.8%)	542 (59.0%)	0.068	0.092	67 (66.3%)	70 (69.3%)	0.047	0.797
Response			0.076	0.109			0.057	0.882
Complete response	26 (23.2%)	247 (26.9%)			24 (23.8%)	26 (25.7%)		
Partial response	36 (32.1%)	228 (24.8%)			32 (31.7%)	31 (30.7%)		
No response	18 (16.1%)	107 (11.6%)			14 (13.9%)	17 (16.8%)		
Not reported	32 (28.6%)	337 (36.7%)			31 (30.7%)	27 (26.7%)		
Margin status			0.037	0.499			0.000	1.000
Negative	100 (89.3%)	849 (92.4%)			94 (93.1%)	94 (93.1%)		
Positive	8 (7.1%)	44 (4.8%)			4 (4.0%)	4 (4.0%)		
Not reported	4 (3.6%)	26 (2.8%)			3 (3.0%)	3 (3.0%)		
Surgical approach			0.064	0.038			0.086	0.218
Open	85 (75.9%)	608 (66.2%)			75 (74.3%)	67 (66.3%)		
MIS	27 (24.1%)	311 (33.8%)			26 (25.7%)	34 (33.7%)		
Nodes retrieved	12.81±8.38	15.01±9.61	0.071	0.168	13.78±8.46	14.38±10.52	0.038	0.811

BMI, body mass index; CCI, Charlson Comorbidity Index; Chemo, chemotherapy; Diff., differentiated; EGJ, Esophagogastric junction; MIS, minimally invasive surgery; SCC, squamous cell carcinoma; SD, standard difference; XRT, radiation therapy.

the younger group. Variability in clinical stage was adjusted in the matched dataset to mitigate the impact of clinical stage on disease-free survival (DFS) and OS.

To study long-term survival outcomes, a second propensity score was performed using all the previous variables in addition to matching for the receipt of AC to reflect a similar treatment course. Ninety-two patients were matched from each group following the abovementioned matching conditions.

Logistic regression was performed for overall complications (*Table 4*), revealing that higher CCI, active smoking (P=0.032),

and longer operations (P<0.001) are significant predictors of increased morbidity. Increasing age (P=0.077) showed a trend but did not reach significance in the univariate model. Cox regression analysis was also performed to confirm the influence of age on RFS and OS (*Table 5*). The significant predictors of RFS were clinical stage (P<0.001), postoperative morbidity (P=0.006), pathologic N+ disease (P<0.001), and AC (P=0.048), whereas the predictors of OS were age (P=0.001), higher CCI, higher clinical stage, postoperative morbidity (P=0.004), and N+ disease (P<0.001).

Kaplan-Meier method was followed to compare RFS and

Table 2 Comparison of surgical outcomes and receipt of adjuvant chemotherapy in young (≤50 years) vs. old (>50 years) patients treated with esophagectomy in the matched dataset

Variables	Young (≤50 years)	Old (>50 years)	HR (95% CI)	P
N	101	101		
Pneumonia	4 (4.0%)	10 (9.9%)	2.665 (0.807–8.797)	0.164
Aspiration	0 (0.0%)	7 (6.9%)	0.482 (0.417–0.558)	0.014*
Pulmonary effusion	9 (8.9%)	16 (15.8%)	1.924 (0.808–4.585)	0.199
ICU admission	8 (7.9%)	10 (9.9%)	1.277 (0.483–3.382)	0.806
Acute kidney injury	6 (5.9%)	5 (5.0%)	0.825 (0.243–2.794)	0.998
Ileus	1 (1.0%)	2 (2.0%)	2.020 (0.180–6.639)	0.561
Delayed gastric emptying	8 (7.9%)	7 (6.9%)	0.866 (0.302–2.484)	0.788
Myocardial infarction	0 (0.0%)	2 (2.0%)	0.895 (0.430–1.569)	0.155
Arrhythmia	5 (5.0%)	24 (23.8%)	5.984 (2.182–16.416)	<0.001*
Atrial fibrillation	5 (5.0%)	10 (9.9%)	2.110 (0.695–6.410)	0.180
Deep venous thrombosis	1 (1.0%)	3 (3.0%)	3.061 (0.313–29.936)	0.621
Pulmonary embolism	3 (3.0%)	2 (2.0%)	0.660 (0.108–4.036)	0.651
Anastomotic leak	6 (5.9%)	9 (8.9%)	1.551 (0.530–4.535)	0.592
Severe reflux	6 (5.9%)	3 (3.0%)	0.474 (0.115–1.952)	0.328
Anastomotic stricture	13 (12.9%)	9 (8.9%)	0.646 (0.263–1.590)	0.373
Superficial wound infection	10 (9.9%)	9 (8.9%)	0.890 (0.346–2.293)	0.810
Bleeding requiring transfusion	1 (1.0%)	1 (1.0%)	1.000 (0.062–10.210)	1.000
Failure to thrive	6 (5.9%)	6 (5.9%)	1.000 (0.311–3.212)	1.000
Overall complications	64 (63.4%)	66 (65.3%)	1.090 (0.613–1.939)	0.883
Reoperation	6 (5.9%)	4 (4.0%)	0.653 (0.179–2.387)	0.748
Discharge on tube feeds	73 (72.3%)	76 (75.2%)	1.137 (0.558–1.987)	0.566
Discharge on TPN	1 (1.0%)	2 (2.0%)	1.011 (0.157–3.861)	0.513
30-day mortality	3 (3.0%)	3 (3.0%)	1.000 (0.197–5.076)	1.000
Receipt of adjuvant therapy	27 (26.7%)	8 (7.9%)	0.366 (0.108–8.294)	0.002*

*, statistically significant. HR, hazard ration; ICU, intensive care unit; TPN, total parenteral nutrition.

OS between these groups (*Figure 1*). The median length of follow up for the entire cohort was 32 months and did not differ between the young or the old groups (32 vs. 34 months; P=0.882). Young patients had comparable RFS (median 49.00±26.03 vs. 27.00±5.44 months; P=0.215) and a trend toward improved OS compared to their older counterparts (median 73.0±28.9 vs. 31.0±6.3 months; log-rank test P=0.073). Life tables suggest a comparable five-year cumulative OS between young vs. old patients (50% vs. 42%). Of note, the majority of recurrences in both age groups occurred within

two years of the surgical resection.

Discussion

The incidence of EC is rising, more rapidly in younger than older patients (2,3,9,23). Previously, it has been suggested that younger patients have a later stage at diagnosis and subsequently have worse outcomes (2,3,7). A SEER analysis from 2004–2013 of EC patients <50 years of age reported a higher likelihood of presenting with stage III/IV disease

Table 3 Ivor-Lewis esophagectomy cohort matched for adjuvant therapies

Variables	Unmatched dataset				Matched dataset 1:1			
	≤50 years	>50 years	SD	P	<50 years	≥50 years	SD	P
N	112	919			92	92		
Sex			0.045	0.151			0.029	0.697
Males	92 (82.1%)	800 (87.1%)			75 (81.5%)	77 (83.7%)		
Females	20 (17.9%)	119 (12.9%)			17 (18.5%)	15 (16.3%)		
Race			0.079	0.163			0.112	0.674
White	102 (91.1%)	882 (96.0%)			87 (94.6%)	88 (95.7%)		
Black	3 (2.7%)	7 (0.8%)			1 (1.1%)	0 (0.0%)		
Hispanic	4 (3.6%)	17 (1.8%)			2 (2.2%)	2 (2.2%)		
Asian	1 (0.9%)	4 (0.4%)			1 (1.1%)	2 (2.2%)		
Other	2 (1.8%)	9 (1.0%)			1 (1.1%)	0 (0.0%)		
BMI	27.42±5.90	28.06±5.53	0.052	0.149				
CCI			0.111	0.012			0.053	0.916
0	14 (12.5%)	48 (5.2%)			8 (8.7%)	7 (7.6%)		
1	19 (17.0%)	126 (13.7%)			15 (16.3%)	12 (13.0%)		
2	28 (25.0%)	212 (23.1%)			20 (21.7%)	21 (22.8%)		
3+	50 (44.6%)	528 (57.5%)			49 (53.3%)	52 (56.5%)		
Missing	1 (0.9%)	5 (0.5%)			0 (0.0%)	0 (0.0%)		
Smoking			0.073	0.063			0.039	0.263
No	41 (36.6%)	251 (27.3%)			32 (34.8%)	28 (30.4%)		
Yes	67 (59.8%)	648 (70.5%)			57 (62.0%)	62 (67.4%)		
Not reported	4 (3.6%)	20 (2.2%)			3 (3.3%)	2 (2.2%)		
Histology			0.076	0.014			0.062	0.397
Adenocarcinoma	95 (84.8%)	844 (91.8%)			77 (83.7%)	81 (88.0%)		
SCC	17 (15.2%)	75 (8.2%)			15 (16.3%)	11 (12.0%)		
Clinical stage			0.134	0.004			0	1.000
0	0 (0.0%)	16 (1.7%)			0 (0.0%)	0 (0.0%)		
I	10 (8.9%)	111 (12.1%)			10 (10.9%)	10 (10.9%)		
IIA	24 (21.4%)	173 (18.8%)			19 (20.7%)	19 (20.7%)		
IIB	10 (8.9%)	120 (13.1%)			9 (9.8%)	9 (9.8%)		
III	45 (40.2%)	335 (36.5%)			38 (41.3%)	38 (41.3%)		
IV	8 (7.1%)	15 (1.6%)			3 (3.3%)	3 (3.3%)		
Unstageable	15 (13.4%)	149 (16.2%)			13 (14.1%)	13 (14.1%)		

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	≤50 years	>50 years	SD	P	<50 years	≥50 years	SD	P
Location			0.026	0.411			0.076	0.300
Distal esophagus	63 (56.3%)	554 (60.3%)			54 (58.7%)	47 (51.1%)		
EGJ	49 (43.8%)	365 (39.7%)			38 (41.3%)	45 (48.9%)		
Grade			0.082	0.071			0.117	0.466
Well diff.	7 (6.3%)	79 (8.6%)			7 (7.6%)	8 (8.7%)		
Moderately diff.	50 (44.6%)	319 (34.7%)			40 (43.5%)	36 (39.1%)		
Poorly diff.	50 (44.6%)	426 (46.4%)			40 (43.5%)	39 (42.4%)		
Not reported	5 (4.5%)	95 (10.3%)			5 (5.4%)	9 (9.8 %)		
Neoadjuvant chemo	89 (79.5%)	627 (68.3%)	0.077	0.047	63 (68.5%)	57 (62.0%)	0.081	0.468
Neoadjuvant XRT	77 (68.8%)	542 (59.0%)	0.068	0.092	62 (67.4%)	57 (62.0%)	0.057	0.742
Response			0.076	0.109			0.091	0.530
Complete response	26 (23.2%)	247 (26.9%)			25 (27.2%)	21 (22.8%)		
Partial response	36 (32.1%)	228 (24.8%)			29 (31.5%)	23 (25.0%)		
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Not reported	32 (28.6%)	337 (36.7%)			28 (30.4%)	35 (38.0%)		
Margin status			0.037	0.499			0.019	0.855
Negative	100 (89.3%)	849 (92.4%)			86 (93.5%)	87 (94.6%)		
Positive	8 (7.1%)	44 (4.8%)			3 (3.3%)	3 (3.3%)		
Not reported	4 (3.6%)	26 (2.8%)			3 (3.3%)	2 (2.2%)		
Surgical approach			0.064	0.038			0.036	0.625
Open	85 (75.9%)	608 (66.2%)			67 (72.8%)	64 (69.6%)		
MIS	27 (24.1%)	311 (33.8%)			25 (27.2%)	28 (30.4%)		
Nodes retrieved	12.81±8.38	15.01±9.61	0.071	0.168				
Adjuvant therapy	33 (29.5%)	114 (12.4%)	0.150	<0.001	19 (20.7%)	21 (22.8%)	0.04	0.588

BMI, body mass index; CCI, Charlson Comorbidity Index; Chemo, chemotherapy; Diff., differentiated; EGJ, esophagogastric junction; MIS, minimally invasive surgery; SCC, squamous cell carcinoma; SD, standard difference; XRT, radiation therapy.

compared to the older group (23). Similarly, a study of a nationwide cancer registry in the Netherlands from 2000 to 2011 by van Nistelrooij *et al*. identified that EC patients ≤50 years of age presented with more advanced disease stage (19). Younger patients in their cohort also presented with more positive lymph node status (70.1% *vs*. 66.4%, P=0.010) and distant metastasis (50.5% *vs*. 44.7%, P=0.047). Hashemi *et al*. suggests that this delay in diagnosis may be due to a postponement of invasive diagnostic measures in young patients presenting with common symptoms such

as dysphagia (7). Similarly, our analysis shows that younger patients indeed present with more advanced disease as they had higher rates of stage III/IV disease, and subsequently higher rates of receipt of NAT.

Postoperative morbidity and complications have been associated with poorer outcomes. In a Swedish prospective population-based study of 275 esophageal patients, Viklund and colleagues analyzed risk factors for complications after resection. Although patient age was not a significant risk factor for developing postoperative complications, pulmonary

Table 4 Results of the univariate and multivariate logistic regression analysis for predictors of overall complications in our patient population

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age	1.012 (0.999–1.025)	0.077		
Race				
White	Referent			
Other	1.767 (0.888–3.515)	0.105		
BMI	1.016 (0.992–1.040)	0.204		
CCI				
0	Referent		Referent	
1	1.753 (1.061–3.596)	0.032*	1.753 (1.190–3.414)	0.037*
2	1.971 (1.116–4.483)	0.019*	1.987 (1.359–3.329)	0.018*
3+	2.599 (1.944–3.709)	0.001*	2.565 (1.877–3.791)	0.001*
NR	0.879 (0.164–4.698)	0.88	0.201 –0.019–2.127)	0.182
Smoking				
No	Referent		Referent	
Yes	1.227 (1.024–1.629)	0.024*	1.230 (1.103–1.677)	0.032*
Not reported	0.846 (0.363–1.970)	0.699	0.457 (0.149–1.405)	0.172
Histology				
Adenocarcinoma	Referent			
SCC	0.890 (0.571–1.388)	0.608		
Clinical stage				
0	N/A			
I	Referent			
IIA	0. 775 (0.485–1.237)	0.285		
IIB	0.864 (0.515–1.449)	0.58		
III	0.716 (0.470–1.090)	0.119		
IV	0.801 (0.315–2.035)	0.641		
Unstageable	0.920 (0.563–1.504)	0.739		
Location				
Distal esophagus	Referent			
EGJ	0.882 (0.679–1.145)	0.346		
Grade				
Well diff.	Referent			
Moderately diff.	0.563 (0.221–1.432)	0.227		
Poorly diff.	0.546 (0.212–1.410)	0.212		
Not reported	0.433 (0.167–1.124)	0.085		

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Neoadjuvant chemo	1.131 (0.848–1.507)	0.402		
Neoadjuvant XRT	0.989 (0.747–1.310)	0.939		
Response				
Complete response	Referent			
Partial response	0.874 (0.610–1.253)	0.465		
No response	0.805 (0.391–1.236)	0.124		
Not reported	0.898 (0.643–1.254)	0.527		
Surgical approach				
Open	Referent			
MIS	0.830 (0.373–1.441)	0.446		
Operative time	1.002 (1.001–1.004)	0.002*	1.004 (1.002–1.005)	<0.001*
Blood loss	1.001 (0.997–1.005)	0.983		
Nodes retrieved	1.002 (1.985–1.019)	0.826		

*, statistically significant. BMI, body mass index; CCI, Charlson Comorbidity Index; SCC, squamous cell carcinoma; EGJ, esophagogastric junction; MIS, minimally invasive surgery; XRT, radiation therapy.

and cardiac complications were most common (24). Similarly, we find that age does not play a role in overall complication rate (63.4% *vs.* 65.3%, P=0.883). However, older patients were more likely to have aspiration (0% *vs.* 6.9%, P=0.014) and cardiac arrhythmia (5.0% *vs.* 23.8%, P<0.001).

In the same nationwide study by van Nistelrooij *et al.*, they assessed clinical outcomes between patients ≤50 and >50 years of age. Although they did identify that younger patients with EC underwent surgery with or without NAT more often as compared to patients >50 years (40.6% *vs.* 37.9%, P=0.047), there were no significant differences in 5-year survival rates after resection (37.6% *vs.* 34.1%, P>0.05) (19). Given the advanced tumor staging in younger patients, more extensive therapeutic efforts are usually justified in clinical practice as younger patients tend to have less comorbidities and, therefore, are considered more fit to receive additional therapy. Our study demonstrates that, despite matching for clinical stage and receipt/response of neoadjuvant therapies, younger patients were three-times more likely to be offered AC over their older peers (26.7% *vs.* 7.9% P=0.002) even after having undergone NAT.

Recent studies have portended the use of AC after esophagectomy stemming from a historical use of perioperative chemotherapy. However, the utility of AC has been debated. Past studies have shown that AC offers improved survival to patients with residual nodal disease (25-28). A NCDB study identified 2,046 esophageal adenocarcinoma patients with lymph node metastases after NAT and esophagectomy, 295 of which received adjuvant therapy. In this propensity-matched cohort, the median survival was 2.6 years with adjuvant therapy and 2.0 years with observation only (28). These results are contrasted by those found by Yerramilli *et al.*, who in a retrospective study of 81 patients, treated with or without chemotherapy following neoadjuvant chemoradiation and esophagectomy found that there were similar rates of three-year OS and RFS (74% *vs.* 70% and 60% *vs.* 64%, respectively) (29). Patients who experienced a complete pathologic response (pCR) on final specimen followed by AC had improved three-year OS, but this was not statistically significant. Another study by Pouliquen *et al.* examined the utility of 5-FU and cisplatin following esophagectomy for squamous cell carcinoma. There was no significant difference in overall survival between the group receiving chemotherapy after surgery compared to those receiving surgery alone (30). Moreover, patients undergoing AC displayed greater renal, neurologic, and hematologic toxicity. Our analysis shows that administration of AC did not necessarily lead to better RFS. While there

Table 5 Results of the multivariate Cox regression analyses for predictors of RFS and OS in our patient population

Variables	Multivariate Cox regression (RFS)		Multivariate Cox regression (OS)	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age			1.004 (1.002–1.005)	0.001*
Race				
White				
Other				
BMI				
CCI			Referent	
0			1.102 (0.922–1.437)	0.437
1			1.558 (1.285–1.992)	0.010*
2			1.939 (1.648–2.312)	0.001*
3+			0.910 (0.258–3.228)	0.881
NR				
Smoking				
No				
Yes				
Not reported				
Histology				
Adenocarcinoma				
SCC				
Clinical Stage				
0	N/A		N/A	
I	Referent		Referent	
IIA	1.519 (0.935–2.466)	0.091	1.589 (0.970–2.603)	0.066
IIB	1.506 (0.844–2.688)	0.166	1.575 (0.871–2.848)	0.133
III	2.605 (1.671–4.063)	<0.001*	2.475 (1.570–3.903)	<0.001*
IV	3.271 (1.928–5.551)	<0.001*	3.237 (1.890–5.544)	<0.001*
Unstageable	1.408 (0.484–4.094)	0.53	1.304 (0.448–3.798)	0.627
Location				
Distal esophagus				
EGJ				
Grade				
Well diff.				
Moderately diff.				
Poorly diff.				
Not reported				

Table 5 (*continued*)

Table 5 (*continued*)

Variables	Multivariate Cox regression (RFS)		Multivariate Cox regression (OS)	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Neoadjuvant chemo				
Neoadjuvant XRT				
Response				
Complete response				
Partial response				
No response				
Not reported				
Surgical approach				
Open				
MIS				
Nodes retrieved				
Postop morbidity	1.474 (1.119–1.942)	0.006*	1.503 (1.136–1.988)	0.004*
Pathologic N status				
Node negative	Referent		Referent	
Node positive	2.155 (1.657–2.802)	<0.001*	2.203 (1.682–2.885)	<0.001*
Missing	1.388 (0.193–9.986)	0.745	1.173 (0.163–8.448)	0.874
Adjuvant therapy	0.674 (0.448–0.998)	0.048*		

*, statistically significant. BMI, body mass index; CCI, Charlson Comorbidity Index; SCC, squamous cell carcinoma; EGJ, esophagogastric junction; MIS, minimally invasive surgery; XRT, radiation therapy.

is a trend towards improved OS in the younger cohort, the survival curves have split far out from surgery, which suggests an age effect rather than disease specific survival. Furthermore, our group has previously found that even when controlling for multiple patient characteristics such as nodal involvement, administration of AC did not provide a survival benefit in all age groups (31). Given the contradicting conclusions, the role of postoperative chemotherapy remains uncertain and requires further elucidation.

There are a few possible explanations for the contradicting survival outcomes in younger patients. Younger patients may indeed have more aggressive tumor biology, as previously suggested, and a more aggressive therapy with the inclusion of AC was necessary to achieve survival outcomes comparable to older patients. Alternatively, there may not be a difference in tumor biology, in which case the additional AC treatment the younger patients received was without benefit. Furthermore, seeing an esophagectomy is a highly

morbid procedure, even in younger patients, the addition AC may hinder their post-operative recovery, leading to a higher morbidity and negating the survival benefit of AC.

Naturally, our study has shortcomings including its retrospective and single institution nature, patient referral, selection bias, and long study period. Our institutional protocol on selecting for patients receiving adjuvant therapy may differ from other places and are not necessarily stated in NCCN guidelines. Nevertheless, it is important to note that despite these considerations, 55% of the young cohort and 63% of older cohort received all non-surgical therapy in the community setting, revealing additional practitioner and patient factors that cannot be adequately captured in a database. Furthermore, we did not explore additional risk factors that may be contributing to time of presentation, treatment options or disease progression. For example, factors such as reflux disease and diet may contribute to disease pathology. There may also be intrinsic
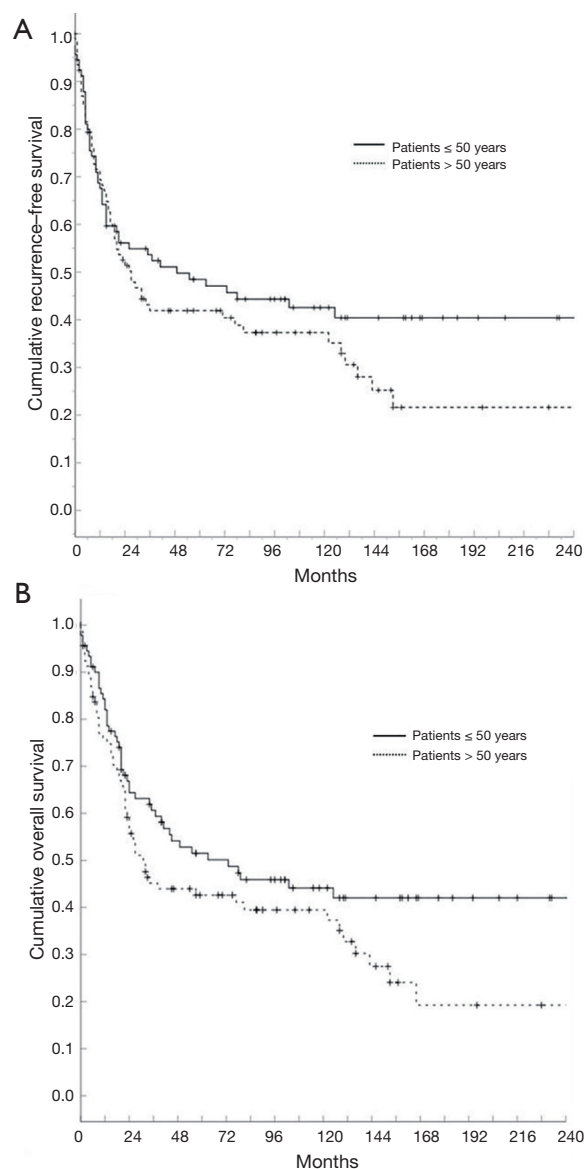
Figure 1 Kaplan-Meier survival curves comparing outcomes between young (≤50 years) *vs.* old (>50 years) patients treated with Ivor-Lewis esophagectomy in the matched dataset. (A) Recurrence-free survival. Median RFS for young patients 49.00±26.03 months *vs.* old 27.00±5.44 months; mean OS for young patients 122.08±13.45 *vs.* old patients 86.53±11.23 months; log-rank test P=0.215. (B) Overall survival. Median OS for young patients 73.00±28.87 months *vs.* old patients 31.00±6.31 months; mean OS for young patients 130.46±13.35 *vs.* old patients 89.09±11.09 months; log-rank test P=0.073. RFS, recurrence-free survival; OS, overall survival.

genetic components to disease progression, which should be investigated in the future. Shifting focus more towards underlying molecular and genetic mechanisms contributing to both response to therapy and long-term outcomes may add granularity (32,33). Developing work has suggested that intratumoral heterogeneity can serve as a potential marker for better response to platinum-based therapy (33). Another challenge is that our surgical dataset is not properly equipped to answer why younger patients may present with more metastatic disease. This question may be better addressed using a NCDB analysis. Despite these limitations, the large power of our study allows us to better understand the natural course of EC. However, the most reliable method of further understanding the relationship between adjuvant therapy in young EC patients would be to perform a prospective study.

In summary, our study supports the notion that younger patients more often present with more advanced EC when compared to an older cohort (2,7,13). Despite matching for stages at presentation, younger patients were more likely to receive adjuvant therapy after esophagectomy compared to older patients, yet that did not necessarily equate to improved outcomes. It is our hope that future projects shed more light on outcomes for younger patients as well as identify more effective therapy options for them.

Conclusions

Younger patients with EC are three-times more likely to be offered AC even when matched for comorbidities, stage, and response to neoadjuvant therapies with their older peers. Survival analysis after matching for receipt of AC demonstrated no difference in RFS between young and old patients, suggesting that AC can be considered for older patients (>50 years) following the same judgment for the younger one, without accounting for chronological age as a limitation.

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Footnote

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