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First, we would like to thank you and thank the respected reviewers for the time they took to read our manuscript entitled "Esophageal Cancer in Young Patients: Does Age Affect Treatment Course and Outcomes?" (Manuscript ID AOE-20-92).

We sincerely appreciate the comments we received from the reviewers. The points they made were very valuable and were very well taken. Following are our responses to the inquiries in the decision letter.

Reviewer A

This study aims to compare disease stage at presentation, treatment modalities, complications and survival between young and older esophageal cancer patients undergoing Ivor Lewis esophagectomy. The authors are to be complemented for this manuscript, which is generally written well. However, the following comments should be addressed:

Comment 1*: Although it seems interesting to investigate the younger population of esophageal cancer patients, it is not clear why 'younger patients' were defined as those being younger than 50 years, especially since the only cited study by Boys et al. had a cut-off age of 40 years. Could the authors please explain their rationale for a cut-off at 50 years?*

Reply 1: We agree that the age cutoff for determination of 'young' vs. 'old' in cancer epidemiology is an area of ongoing debate. As mentioned in our manuscript, some studies used the cutoff of <40 years as a reference for Adolescents and Young Adults (AYA) in line with the SEER reporting. Other studies used different age cutoffs based on the distribution of their patients' age groups.

However, in our study, we elected to use the cutoff of <50 years in line with the American Cancer Society (ACS) epidemiology reporting that indicates a <10-fold probability of esophageal cancer occurrence and mortality in patients <50-year-old. Several other studies have set the precedent of utilizing 50 years as a cutoff based on the distribution of patient age groups. Moreover, our practice at our institution is to recommend genetic testing for patients with a new diagnosis of esophageal cancer even though this recommendation is not yet adopted by the National Comprehensive Cancer Network (NCCN). Despite the fact that most of our patients in our group did not have genetic syndromes, we believe using the age cutoff <50 years would reasonably differentiate young vs. old for consideration of a different genetic origin or biologic behavior. We elaborated on the rationale of selecting the age cutoff in the Methods paragraph to further clarify to the readers.

"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 esophageal cancer 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 esophageal cancer, 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."

Comment 2*: Although PSM is a great way to compare distinct groups, it is methodologically questionable to create groups based on age mainly because a cut-off (in this case 50 years) is quite arbitrary. Alternative strategies, such as multivariable logistic regression analysis, would allow entering age as a continuous parameter to evaluate its impact on the selected outcome (e.g., complications). Please explain why the choice was made to categorize patients based on age*.

Reply 2: Thank you for the suggestion. The goal of using PSM was to achieve a strict adjustment of all baseline characteristics between the groups of the study to minimize the influence of confounding factors particularly on RFS and OS in the Kaplan Meier analysis. The authors believed it would be the procedure of choice for that purpose given the relatively small size of the study group (N=112).

However, we agree that for comparison of other outcomes, such as operative morbidity, a logistic regression would be necessary, and the use of age as a continuous variable would provide more clarity to the impact of age on such outcomes. Therefore, we performed a logistic regression analysis for overall complications (Table 4) and concluded that higher CCI, active smoking, and longer operations are significant predictors of increased morbidity. Increasing age showed a

trend but did not reach significance in the univariate model. In addition, to confirm the influence of age on RFS and OS, Cox regression analyses were also performed (Table 5). The predictors of RFS were clinical stage, postoperative morbidity, pathologic N+ disease, and adjuvant chemotherapy, whereas the predictors of OS were age, CCI, clinical stage, postoperative morbidity, and N+ disease. These changes were reflected in the revised manuscript including the added tables and the associated discussion in the results section for these new findings.

"Logistic regression was performed for overall complications (Table 5), 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. The predictors of RFS were clinical stage ($p<0.001$), postoperative morbidity ($p=0.006$), pathologic N+ disease ($p<0.001$), and adjuvant chemotherapy ($p=0.048$), whereas the predictors of OS were age ($p=0.001$), higher CCI, higher clinical stage, postoperative morbidity ($p=0.004$), and N+ disease ($p<0.001$)."

Comment 3*: According to the aims stated in the introduction, this study (amongst other things) aims to compare disease stage at diagnosis. In that case, it seems that the age groups should be matched and subsequently compared for cTNM stage, as has been done for complications and survival. Please clearly state the research questions and provide the appropriate analyses required to answer them*.

Reply 3: The stated aim of comparing clinical disease stage between young and old patients stems from the hypothesis that younger patients tend to have a more aggressive biology, thus might present at more advanced stage of their disease which indicates more intensive treatment, and possible poorer outcomes in general. To investigate, table 3 demonstrates a variability in the clinical stage at presentation between the young and old groups. Young patients had higher rates of stage IV (7.1% vs. 1.6%), and somewhat comparable rates of other stage distribution. It is difficult, based on this observation, to draw a definitive conclusion and state that young patients tend to have more advanced disease at presentation. Variability in clinical stage was adequately adjusted in the matched dataset to mitigate the impact of clinical stage on DFS and OS, especially after proven significant in the added Cox regression analysis.

"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 the younger group. Variability in clinical stage was adjusted in the matched dataset to mitigate the impact of clinical stage on DFS and OS."

Comment 4*: How were postoperative complications defined? Were the ECCG recommendations used? Especially complications such as 'failure to thrive' deserve to be clearly defined in the methods*.

Reply 4: Thank you for the suggestion. The postoperative complications described in our results are consistent with the basic platform of complications described by the ECCG. While failure to thrive is not included in the ECCG discussion, we find that it is worth noting as it has been documented before in the literature. We use the United States National Institute of Aging definition of 'failure to thrive', which is described as a "syndrome of weight loss, decreased appetite and poor nutrition, and inactivity, often accompanied by dehydration, depressive symptoms, impaired immune function, and low cholesterol." We find that this often corresponds with patients, who despite having no clear diagnosis and no evidence of severe malnutrition, start to decline in functional status. We have incorporated this description into our methods section.

"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)."

Comment 5*: Was there any difference in the overall severity (Clavien-Dindo) of complications between the age groups? One could hypothesize that younger patients have less severe sequelae of complications. Please provide this information if possible*.

Reply 5: Thank you for the comment and suggestion. Our postoperative data shows that the rates of overall morbidity did not differ between young and old patients in the matched dataset (63% vs. 65%; $p=883$). 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. An elaboration on these findings was added to the manuscript to further explain to the readers.

"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 adjuvant chemotherapy despite identical clinical staging and response to neoadjuvant therapy (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."

Comment 6*: Please be more specific on the institutional protocol regarding patient selection for (neo)adjuvant treatment. As the study period is more than 2 decades, it probably changed substantially over time. Therefore, patients should probably also be matched regarding year of diagnosis or treatment.*

Reply 6: Thank you for the comment. We were early adopters on delivering neoadjuvant therapy (NAT) for patients with "locally advanced" gastroesophageal cancers. NAT was provided for patients with T2 or nodal positive disease as defined by CT, PET or endoscopic ultrasound that was performed selectively for early lesion (smaller) starting in 1994 and more routinely for all patients starting in 2000. We incorporate the discussion on our institutional protocol in our methods section.

"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."

Comment 7*: Please report the total median follow-up for the entire cohort and for the different subgroups that are compared. Was there a difference in total follow-up between the groups?*

Reply 7: Thank you for a very valuable comment. 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 months vs. 34 months; p=0.882). We added a sentence to 'Results' to report the length of follow up.

"Kaplan-Meier method was followed to compare RFS and 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 months vs. 34 months; p=0.882)."

Comment 8*: The authors conclude that young patients are 3 times more likely to receive AC when compared to older patients. If this finding persists after addressing the previous methodological comments, it should be emphasized that it is based on a single center's experience. The institutional protocol on adjuvant therapy may have been different than in other centers, which means that the findings may not be generalizable.*

Reply 8: We agree with the reviewer's astute comment. Indeed, this is a single institution experience despite the fact that neither institutional "protocols" nor NCCN guidelines call for additional "adjuvant" therapy after neoadjuvant therapy. Nevertheless, it is important to note that despite these considerations, 55% of the younger and 63% of the older patients in the community setting are treated with both NAT and adjuvant therapy and our study aims to further elucidate this discrepancy. We include this discussion in the limitations section of the discussion.

"Naturally, our study has shortcomings including its retrospective and single institution nature, patient referral, and 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."

Reviewer B

The authors of the study investigated the impact of younger age on the outcomes of esophagectomy for esophageal cancer. They found that young patients tend to present with more advance disease and are more likely to be offered adjuvant chemotherapy.

After adjusting for receipt of adjuvant therapy, they have similar overall survival as compared to their older counterparts. I congratulate the authors for their fine work. The manuscript is very well-written and the topic is indeed interesting. The main limitations of the study (e.g., selection bias and long study period) are well addressed in the manuscript.

***Comment 1**: Including the presence or not of underlying Barrett´s Esophagus in the pathology report of both groups might be interesting*.

Reply 1: We agree that the presence of Barrett's on final pathology would be an interesting finding to report. In the unmatched dataset, Barrett's was reported in 41.4% young specimens vs. 44.4% old specimens (p=0.838). In the matched dataset, the rates were 42% vs. 40% (p=0.335). A note describing these findings was added to the Results paragraph.

"Presence of Barrett's esophagus was not statistically significant between young and old specimens for both unmatched (41.4% vs. 44.4%, p=0.838) and matched (42% vs. 40%, p=0.335) patients."

***Comment 2**: The number of nodes retrieved is included in the tables. Is it possible to include the number of positive nodes/ratios in both groups?*

Reply 2: The ratio of positive/retrieved nodes is an interesting concept in GI malignancies, especially in esophagus, stomach, and pancreas.
Below is a summary of our data regarding positive nodes and the ratio, in the unmatched and matched datasets of young vs. old patients.

	Unmatched			**Matched**		
	Young	Old	p	Young	Old	p
Positive N	1.37±2.43	1.02±2.44	0.160	1.24±2.25	1.31±2.59	0.843
Ratio	0.14±0.25	0.08±0.19	0.010	0.11±0.21	0.12±0.23	0.752

These findings were also added to the Results paragraph for their significance to the topic at hand.

"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)."

***Comment 3**: I assume young patients might have shorter time-interval between neoadjuvant therapy and surgery, and between surgery and adjuvant therapy as they often recover faster from the systemic therapy and esophagectomy, respectively. Although the ideal time-interval is a topic under discussion, this time may effectively affect outcomes. Adding this information and discussing it in the manuscript would contribute significantly to the literature.*

Reply 3: We appreciate the insight and agree that it would be very interesting to look at this trend. However, we unfortunately do not have the specific interval for all patients available to make any meaningful conclusions.

Reviewer C

Thank you for allowing me to review this well written and thoughtful manuscript. There have been numerous papers comparing outcomes based on age and outcomes for esophageal cancer. This is a well thought out approach to aim to identify the outcomes of younger patients. I have a few minor questions:

***Comment 1**: Why did you choose 50 years as your age cut-off? It looks some publications have chosen 40, 45 and 50. Was there any reason you decided on 50?*

Reply 1: We agree that the age cutoff for determination of 'young' vs. 'old' in cancer epidemiology is an area of ongoing debate. As mentioned in our manuscript, some studies used the cutoff of <40 years as a reference for Adolescents and Young Adults (AYA) in line with the SEER reporting. Other studies used different age cutoffs based on the distribution of their patients' age groups.

However, in our study, we elected to use the cutoff of <50 years in line with the American Cancer Society (ACS) epidemiology reporting that indicates a <10-fold probability of esophageal cancer occurrence and mortality in patients <50-year-old. Several other studies have set the precedent of utilizing 50 years as a cutoff based on the distribution of patient age groups. Moreover, our practice at our institution is to recommend genetic testing for patients with a new diagnosis of esophageal cancer even though this recommendation is not yet adopted by the National Comprehensive

Cancer Network (NCCN). Despite the fact that most of our patients in our group did not have genetic syndromes, we believe using the age cutoff <50 years would reasonably differentiate young vs. old for consideration of a different genetic origin or biologic behavior. We elaborated on the rationale of selecting the age cutoff in the Methods paragraph to further clarify to the readers.

"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 esophageal cancer 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 esophageal cancer, 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."

Comment 2*: The younger patients have more SCC but not more smoking or African Americans, any explanation or hypothesis as to why that is?*

Reply 2: Thank you for the comment. Indeed, it is a very interesting question that has no clear answer. We believe that it could be due to a variety of factors, such as alcohol intake, HPV status, or immunosuppression. Due to the limited sample size within our database, it is hard to delineate an answer. Another potential reason is that as we use a surgical database, older patients with SCC may not have been referred for surgical consultation or may have declined surgical management if there was a chance for complete response with chemoradiation. However, this is an interesting question that merits further study.

Comment 3*: What new information does this research add to the current available literature?*

Reply 3: Thank you for the comment. There is an expanding amount of literature studying the role of age in esophageal cancer patients. In our study, we shed light on the nuances of potential overuse of adjuvant therapy in younger patients who receive neoadjuvant therapy and show no necessary benefit in overall survival. 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. We hope that this finding can allow clinicians to investigate more effective therapies for younger patients or stimulate further investigation on this phenomenon of adjuvant therapy usage in patients <50 years.