Peer Review File

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Reviewer A Comment: The authors present an excellent retrospective analysis of the National Cancer database outcomes for patients who underwent either upfront surgery vs neoadjuvant approach in esophageal adenocarcinoma. They also performed a subset analysis with patients 80+ years of age and with higher comorbidity status. These showed that even these subsets benefit for induction therapy with regards to long term survival and margin status. The methodology is sound and may have been strengthened by utilizing a propensity matched analysis of patients 80+ who had induction therapy to those less than 80 years who underwent induction therapy. The ability to tolerate induction therapy may be an independent predictor of better performance status in the 80+ group. The authors do address this point in their limitations and as such the propensity match is not an absolute. Overall, this is one of the few papers that provides insight into esophageal adenocarcinoma outcomes and is very relevant to the North American and European populations. I would be in favor of publishing this manuscript.

RESPONSE: We very much appreciate the reviewer's insightful comments and positive feedback.

CHANGES TO THE TEXT: None needed.

Reviewer B General Comment: In the paper titled "Is Induction Therapy Optimal for All Patients with Locally Advanced Distal Esophagus Adenocarcinoma? The Impact of Age and Co-Morbidities on Treatment and Outcomes," the authors perform an analysis of nearly 14 thousand patients in the database to evaluate the outcomes of older patients undergoing induction therapy for locally advanced disease. The authors demonstrated improved outcomes, even in patients greater than 80 years of age, while also demonstrating that older patients are less likely to receive induction therapy. This is an important study in the field, reinforcing the importance of induction therapy in frail and elderly patients.

RESPONSE: We appreciate the reviewer's concise summary of our findings, and also their positive comment.

CHANGES TO THE TEXT: None needed for this comment.

Reviewer B Comment 1: Line 51 – what has it risen from?

RESPONSE: In response to the comment, the introduction section of the manuscript has been revised to state "The estimated new cases of esophageal cancer in the United States have risen from 17,460 in 2012 to 21,560 in 2023"

CHANGES TO THE TEXT: Lines 88-90 now contain this new statement.

Reviewer B Comment 2: Line 53 – it would be beneficial for the reader to report the survival of patients with locally advanced disease (your inclusion criteria) over time.

RESPONSE: In response to the comment, the introduction section of the manuscript has been revised to state "Five-year survival rates have consistently improved from 11.5% in 1995, but still remains disappointingly low at 21.7% overall in a recent study [4]."

CHANGES TO THE TEXT: Lines 88-90 now contain this new statement.

Reviewer B Comment 3: Line 54 – 57 – Very long and run-on. Revise to: Poor outcomes are partially attributed to delayed diagnosis, as most patients do not develop symptoms until the cancer has become at least locally advanced.

RESPONSE: In response to the comment, that sentence in the introduction of the manuscript has been revised to include the suggested statement.

CHANGES TO THE TEXT: Lines 91-92 now contain this new statement

Reviewer B Comment 4: Line 61 – 64 – run on sentence. Revise into 2 sentences.

RESPONSE: In response to the comment, the manuscript has been revised so that the previous sentence has been revised to "The Chemoradiotherapy for Oseophageal Cancer Followed by Surgery Study (CROSS) in particular showed a survival benefit of induction chemoradiation plus surgery over surgery alone for patients with adenocarcinoma of the esophagus or EGJ [1]. This landmark trial significantly impacted guideline treatment recommendations [1]."

CHANGES TO THE TEXT: Lines 97-99 now contain these new 2 sentences.

Reviewer B Comment 5: Line 67 – another run on sentence. Cut previous sentence after timely surgery. Revise the following sentence to: In this scenario, one may suspect that these patients' oncologic outcomes could have been better if they proceeded straight to surgery without receiving induction therapy.

RESPONSE: In response to the comment, the introduction section of the manuscript has been revised as suggested, and now states "These patients' oncologic outcomes may be better if they proceed straight to surgery without receiving induction therapy [9,10]."

CHANGES TO THE TEXT: Lines 103-105 now contains this new sentence.

Reviewer B Comment 6: Line 79 – add comma before thus.

RESPONSE: In response to the comment, the manuscript has been revised to include the suggested comma.

CHANGES TO THE TEXT: Line 115 now contains this comma.

Reviewer B Comment 7: Line 82 – AJCC needs citation/

RESPONSE: In response to the comment, the manuscript has been revised to include this citation: Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction. Ann Surg Oncol . 2010 Jul;17(7):1721-4

CHANGES TO THE TEXT: Line 121 and lines 491-492. Note that the subsequent numbering of citations in the manuscript has been revised as necessary to reflect the additional of a new citation.

Reviewer B Comment 8: Line 84 - “potentially curative” is quite vague. Could you elaborate?

RESPONSE: In response to the comment, the patient selection portion of the methods section has been revised to better clarify which patients were included for analysis, and now states “We included only patients who had primary surgery with or without post-operative chemotherapy or radiation, patients with preoperative chemoradiation followed by surgery, or patients treated with chemoradiation alone. Patients who received either chemotherapy alone or radiation therapy were not included, as these treatment regimens are generally not considered potentially curative for locally advanced esophageal cancer. “

CHANGES TO THE TEXT: Lines 123-125 now contains these sentences.

Reviewer B Comment 9: Line 87 – remove “has been shown to be” and replace with ‘is’

RESPONSE: In response to the comment, the manuscript has been revised per the reviewer suggestion and this sentence now states “Because the predominant induction therapy practice for esophageal adenocarcinoma is induction chemoradiation,…”

CHANGES TO THE TEXT: Lines 125-126 contain the revised sentence.

Reviewer B Comment 10: Line 90 – known use of surgery is an odd wording. Please revise.

RESPONSE: In response to the comment, the manuscript has been revised so that the sentence in question has been clarified as follows: “Only patients for whom the use and sequence of surgery, chemotherapy, and radiation was explicitly recorded in the dataset were included for analysis, and patients with any previous malignancy or incompletely recorded follow-up data were excluded.”

CHANGES TO THE TEXT: Lines 130-131.

Reviewer B Comment 11: Line 91 – previous malignancies – did you exclude skin cancer?

RESPONSE: In response to the comment, the manuscript has been revised to clarify that patients with skin cancer were excluded from the analysis by revising the statement in question to state: “patients with any previous malignancy or incompletely recorded follow-up data were excluded.”

CHANGES TO THE TEXT: Line 132.

Reviewer B Comment 12: Line 94 – remove ‘potentially’

RESPONSE: In response to the comment, the manuscript has been revised to so that the word "potentially" was removed from the sentence in question as suggested.

CHANGES TO THE TEXT: Line 135.

Reviewer B Comment 13: Line 95 – replace 'was' to 'sought to analyze ...'

RESPONSE: In response to the comment, the manuscript has been revised so that the word "was" has been replaced by "sought" in the sentence in question as suggested.

CHANGES TO THE TEXT: Line 137.

Reviewer B Comment 14: Methods – Please review and reduce redundancy in language.

RESPONSE: We appreciate the reviewer's careful reading of the manuscript and their suggestions for us to clarify the text. We have made revisions as suggested, but also wish to make sure that the manuscript contains enough detail for readers to re-create the study if they wish to examine or build on this analysis.

CHANGES TO THE TEXT: Lines 115, 121, 123-126, 130-132, 135, 137, 170-172.

Reviewer B Comment 15: Line 126-128 – abbreviate sentence or remove completely.

RESPONSE: In response to the comment, the manuscript has been revised to abbreviate the sentence in question, which now reads "The subgroup analyses were performed to investigate outcomes in patients who generally would be considered higher risk for aggressive surgery even in the absence of using preoperative treatment."

CHANGES TO THE TEXT: Lines 170-172.

Reviewer B Comment 16: Line 145 – remove entire cohort from title.

RESPONSE: In response to the comment, the manuscript has been revised to remove "entire cohort" as suggested.

CHANGES TO THE TEXT: Line 192.

Reviewer B Comment 17: Line 148 – remove "time" from sentence.

RESPONSE: In response to the comment, the manuscript has been revised to remove "time" as suggested.

CHANGES TO THE TEXT: Line 196.

Reviewer B Comment 18: Line 158 – revise to “were associated with a lower use of induction chemoradiation”

RESPONSE: In response to the comment, the manuscript has been revised as suggested such that the sentence in question now states “…were associated with a lower use of induction chemoradiation…”

CHANGES TO THE TEXT: Lines 207-208.

Reviewer B Comment 19: Line 160 – replace ‘in the entire cohort’ to ‘overall’

RESPONSE: In response to the comment, the manuscript has been revised as suggested such that the sentence in question now states “Induction therapy overall was associated…”

CHANGES TO THE TEXT: Line 209.

Reviewer B Comment 20: Methods – add that continuous variables are reported as median (IQR) and adjust as needed in results.

RESPONSE: The reviewer is correct that continuous variables were reported as the median with the interquartile range, and tn response to the comment, the methods section of the manuscript has been revised to explicitly state this.

CHANGES TO THE TEXT: Lines 187-188.

Reviewer B Comment 21: Line 222-224 - run-on sentence. End first sentence at “primary surgery” and begin new sentence.

RESPONSE: In response to the comment, the manuscript has been revised to split the sentence in question into two shorter sentences.

CHANGES TO THE TEXT: Line 285.

Reviewer B Comment 22: Line 226 – revise to explicitly state what these associations were, and reduce redundancy in following sentences.

RESPONSE: In response to the comment, the manuscript has been revised to clarify the association of age and comorbidity scores with treatment and outcomes while reducing redundancy, and the sentences in question now read: “Increasing age and higher co-morbidity scores were both associated with patients being more likely to go straight to surgery, perhaps reflecting concerns by their treatment teams regarding patients’ ability to tolerate tri-modality therapy. Increasing age and higher co-morbidity scores were also associated with worse survival in the cohort. However, subset analysis of both patients over the age of 80 and patients with Charlson comorbidity scores of 2 or higher continued to show that patients with induction chemoradation had better survival than patients who had primary surgery. “

CHANGES TO THE TEXT: Lines 287-290

Reviewer B Comment 23: Methods – would it be possible to propensity match the two groups? Chemoradiation alone versus induction and surgery group?

RESPONSE: We appreciate the reviewer's comment on the statistical analysis, and reviewer 1 also brought up the possibility of using propensity matching as an additional method of investigating our findings. However, reviewer A did also comment that propensity matching was not absolutely necessary to support the findings in the study, and we strongly agree with Reviewer A. First, we are aware of criticisms that propensity score analysis are overused in surgical studies (including in a discussion at the 2024 Society of Thoracic Surgeons Meeting, on Thoracic Surgery Research Datasets). In addition, our goal was to investigate the impact of induction therapy specifically in the subgroups of elderly patients and patients with high-comorbidity scores. We don't think the use of propensity matching in the entire cohort would provide benefit to these analyses. In addition, we are very aware of the risk of the Propensity Score Matching paradox, where overuse of this analytical method can actually lead inaccurate or misleading results when pre-existing covariate balance is good, due to the methods increasing imbalance and bias rather providing better control. In the very important subgroup analyses of elderly patients and those with comorbidities, we have already inherently created balanced groups based on our analytical criteria, in addition to also already having limited the cohort to locally advanced stages. The characteristics of the patients in these subgroups are generally well balanced, particularly in the most important parameters, as shown in tables 4 and 8, and as such we feel that the use of logistic regression and multivariable survival analysis are adequate to supplement and further investigate the findings from our univariate analyses.

CHANGES TO THE TEXT: None

Reviewer B Comment 24: Line 243-244 – did you compare outcomes between SCC versus adenocarcinoma to accurately make this statement?

RESPONSE: We appreciate the reviewer's alluding to the fact that grouping both squamous cell carcinoma and adenocarcinoma patients as "esophageal cancer" is no longer appropriate in terms of staging and management. In our study, we only included adenocarcinoma patients and thus did not try to make any comment on management or outcomes of squamous cell carcinoma patients. In the discussion paragraph that contains lines 243-244 as referenced by the reviewer, we are mostly just discussing findings from previous published studies of the CROSS trial, and trying to interpret the findings from those studies in light of the findings of our study. Lines 243-244 in our manuscript only try to highlight that our study supports the use of induction therapy even in older patients and those with more co-morbidities. In response to the reviewer's comment, we have revised the statement to try to make this more clear: "However, our current study's findings do support continued use of a CROSS trial regimen over primary surgery in locally advanced esophageal adenocarcinoma patients, even those who are elderly or have significant co-morbidities."

CHANGES TO THE TEXT: Lines 308-310

Reviewer B Comment 25: Line 251 – 24 – Very long run-on sentence which is confusing. Please revise and form two sentences. Please focus on brevity and be to the point.

RESPONSE: In response to the comment, the section of the manuscript referenced has been revised to hopefully be more clear and succinct, and now reads: "The finding that primary surgery patients did better than those patients treated with chemoradiation alone in both higher risk subsets does suggest that some subset of patients may indeed be better off going straight to surgery. Induction chemoradiation does have a risk of peri-treatment mortality associated with it, and approximately 20% of patients may never make it to surgery [9,10,21]. However, a decision to forego induction chemoradiation can compromise survival and must consider specific patient details regarding their ability to tolerate therapy beyond generalized categories such as an age limit or the presence of co-morbidities. Overall, our results suggest that this should not be standard practice and patient management ideally would focus on supportive care that facilitates patients tolerating multimodal therapy. Proceeding with surgery without chemoradiation should only be done after careful and detailed multidisciplinary evaluation of a patient's ability to tolerate all modalities of therapy."

CHANGES TO THE TEXT: Lines 318-328.

Reviewer B Comment 26: Line 260 – Which patients should be considered for chemoradiation therapy alone?

RESPONSE: We appreciate this insightful clinical comment from the reviewer, which is certainly a very important patient management issue. In our clinical experience, we would generally only favor chemoradiation alone for esophageal adenocarcinoma in those patients who either do not wish to pursue surgery or are deemed inadequate surgical candidates based on their medical condition and functional status. Unfortunately, this clinical issue is not investigated at all in our study, and we don't think it would be appropriate to speculate about that management decision in our manuscript. We do appreciate, though, that a future study that investigates that topic could be very helpful to the esophageal cancer community.

CHANGES TO THE TEXT: None

Reviewer B Comment 27: Line 262-265 – run-on sentence. Plese revise.

RESPONSE: In response to the comment, the manuscript has been revised such that sentence in question has been revised into multiple sentences to be more succinct and clear: "However, patients who proceed with primary surgery for locally advanced esophageal adenocarcinoma have a low chance of cure with surgery alone. As these patients may benefit from adjuvant therapy, the same considerations of whether patients could tolerate surgery followed by systemic therapy must also be carefully evaluated in this situation [22]. "

CHANGES TO THE TEXT: Lines 329-332

Reviewer B Comment 28: Line 267 – 29270 – Surgical approach is not the concern of this study, would advise removing discussion on ERAS as it does not add to the paper.

RESPONSE: We appreciate that insight from the reviewer, and as suggested that discussion has been removed from the revised manuscript.

CHANGES TO THE TEXT: Line 335.

Reviewer B Comment 29: Line 278 – This raises an important question of QoL. It would be helpful to add evidence based findings based on your literature search re: quality of life in patients receiving induction therapy. While 4% difference is statistically significant, how can we weigh the risks and benefits of aggressive treatment with marginally improved survival rates?

RESPONSE: We appreciate the reviewer's clinical insight, and certainly also appreciate that a patient's decision regarding whether the benefits of aggressive therapy, particularly esophagectomy, is worth the risks, the peri-treatment discomfort, and the post-surgery dietary and lifestyle changes is a very personal process. Unfortunately, the literature is quite sparse and limited regarding this topic, and also beyond the scope of our particular study.

CHANGES TO THE TEXT: None.

Reviewer C General Comment: The authors' manuscript "Is Induction Therapy Optimal for All Patients with Locally Advanced Distal Esophagus Adenocarcinoma? The Impact of Age and Co-Morbidities on Treatment and Outcomes " is an excellent addition to the literature on management of esophageal cancer. This work should be of broad interest to the Journal of Thoracic Disease readership. The study is concise, well designed, well written, and highly relevant to current practice. I recommend acceptance without revision.

RESPONSE: We greatly appreciate the reviewer's positive assessment of our study

CHANGES TO THE TEXT: None required.

Reviewer C Comment 1: Page 6, line 179: Consider changing "survival in the over 80 surgical patients" to "survival in octogenarian surgical patients" or "survival in the age over 80 surgical patients" Although, I understood the meaning based on the paper's context, it could be misinterpreted as referring to the number of patients rather than their age.

RESPONSE: We appreciate the reviewer pointing out the potential confusion that could result from the way we labeled that section of the results section, and In response to the comment have revised the title as suggested to "Peri-operative Outcomes and Survival in the Age over 80 Surgical Patients".

, the manuscript has been revised to

CHANGES TO THE TEXT: Line 229.

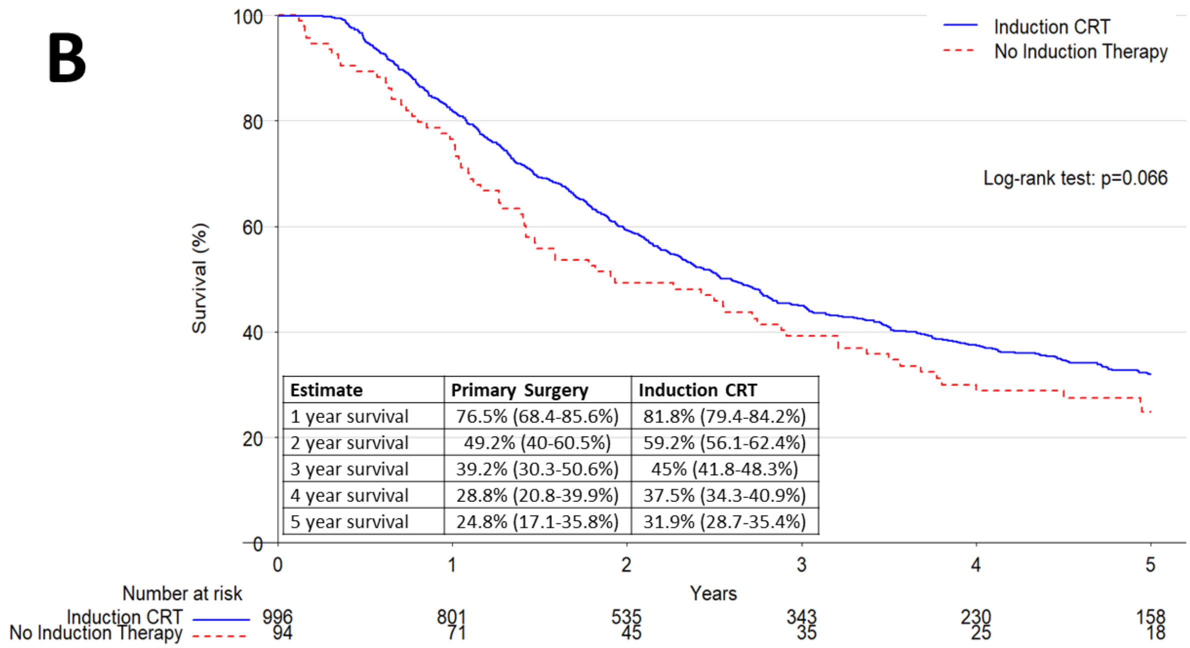
Reviewer C Comment 2: Page 16, line 396: typo "vor"

RESPONSE: We appreciate the reviewer's very careful reading of our paper, and have In response to the comment revised the manuscript to correct the typo ("vor" has been changed to "versus").

CHANGES TO THE TEXT: Line 406.

Reviewer C Comment 3: Page 25 Figure 5B is mislabeled as A.

RESPONSE: We again appreciate the reviewer's careful reading of the paper, and realize that we missed the fact that figure 5 just showed panel A twice, and our intended panel B was not compiled with the manuscript. We will ensure that revised manuscript contains the appropriate Figure5B, which is:



Estimate	Primary Surgery	Induction CRT
1 year survival	76.5% (68.4-85.6%)	81.8% (79.4-84.2%)
2 year survival	49.2% (40-60.5%)	59.2% (56.1-62.4%)
3 year survival	39.2% (30.3-50.6%)	45% (41.8-48.3%)
4 year survival	28.8% (20.8-39.9%)	37.5% (34.3-40.9%)
5 year survival	24.8% (17.1-35.8%)	31.9% (28.7-35.4%)

CHANGES TO THE TEXT: The correct Figure 5B will be uploaded with the revised manuscript.

Reviewer D Comment 1. Adjuvant Tx. did not have any prognostic impact for the patients? You focused neo-adjuvant chemoradition therapy. However there was no results about adjuvant Tx. All of the patients received the adjuvant Tx or not?

RESPONSE: We appreciate the reviewer bringing up this very important point. Table 6 of the manuscript does specify the rates of post-operative chemotherapy use in the age over 80 subset as well as the subset with the comorbidity score of 2+. To address the reviewer comment, we have revised the text of the results section of the age over 80 subset to include this statement: "Post-operative chemotherapy use was uncommon in all of the age over 80 patients, but patients who had primary surgery were more likely than induction chemoradiation patients to get post-operative chemotherapy (14.6% [12/82] vs 1% [2/206], p<0.001)."; and the results section of the high co-morbidity patients to include this statement: "Primary surgery patients were much more likely to be given post-operative chemotherapy as compared to the induction chemoradiation patients (46.8%

[44/94] vs 5.6% [56/996], p<0.001), though adjuvant chemotherapy was used in the minority of both groups."

CHANGES TO THE TEXT: Lines 237-240 and lines 272-274.

Reviewer D Comment 2. The patients with primary surgery were more common in early phase of this study and the survival was lower in your study. Surgical technique is not different? Open surgery, minimally invasive surgery or robotic surgery -> there was no descriptions regarding the surgery. Lymph node dissection is also important for esophageal cancer surgery -> there was no significant different?

RESPONSE: We appreciate the reviewer's clinical insight, and agree surgical techniques and peri-operative management have changed over the relatively long time-period of the study. Unfortunately, the use of minimally invasive techniques for surgery was not recorded in the earlier time period of the study, and so we cannot factor that detail into our analysis. In response to the comment, the manuscript has been revised to specifically acknowledge this limitation in the discussion section, by adding this statement: "In addition, surgical techniques and peri-operative care for esophagectomy patients have improved with time, and the finding that primary surgery was more common earlier in the time course of the study could provide a bias against the primary surgery patients. ". In regards to lymph node dissection, table 6 of the manuscript does show that primary surgery patients in both higher-risk subsets had more nodes harvested (median 16 vs 14, p=0.03 in the over 80 group and median 17 vs 14, p=0.001 in the high co-morbidity score group), despite the primary surgery approach being more common in the earlier part of the study, when the importance of lymph node dissection might not have been as well appreciated. However, we think our finding is consistent with other studies that show less lymph nodes are typically identified in the surgical specimen when induction therapy has been used.

CHANGES TO THE TEXT: Lines 352-355