

## Peer review file

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### Reviewer A

The authors compare the three interventions- nutritional counseling, J-tube, and stent placement, and find that the patients receiving stents had a lower %TWL and were associated with more procedural complications. Additionally, no intervention use was found to be a better initial nutritional strategy for curative-intent patients, as they were reported to maintain adequate weight in the absence of any intervention.

Although not placing any intervention before neoadjuvant therapy has been the precedent, this study adds to the existing literature by addressing how the patients receiving only nutritional counseling fare against those receiving intervention for dysphagia.

**Comment A.1:** The manuscript could be further strengthened by addressing the following point: We recommend adding a multivariable model that adjusts for the variables of the stage, tumor, age, performance status, and smoking status.

Reply A.1: In response to the reviewer's comment, we tried this. However, with a sample size of 20 stent patients and 39 J-tube patients, multivariable modeling was not feasible. We have revised the language in the Discussion under Limitations.

Changes in the text A.1: Line 281

**Comment A.2:** The manuscript could be further strengthened by addressing the following point: There is the possibility that healthier patients with the smaller size of tumors, a higher body mass index, etc. are more likely to be in the nutritional counseling group as compared to the patients in a relatively poor state of health. The authors should address this issue to reduce selection bias.

Reply A.2: We believe the reviewer meant to say, "There is the possibility that healthier patients with the smaller size of tumors, a higher body mass index, etc. are more likely to be in the nutritional counseling group as compared to the patients *in the stent and J-tube groups*." We regret that our discussion of the limitations was not more transparent. When we discussed randomized controlled trials, we were referring to selection bias. We have revised the text to make it explicit.

Changes in the text A.2: Line 286 and lines 293-302.

### Reviewer B

The authors perform a retrospective review to determine the effectiveness of jejunostomy tube, esophageal stent, or no intervention for esophageal cancer patients undergoing neoadjuvant therapy. Perioperative nutrition is an important topic for esophageal cancer patients and of

interest to thoracic surgeons and oncologists. I have several comments to improve the manuscript.

**Comment B.1:** There is likely selection bias between groups and this is a major limitation which should be discussed.

Reply B.1: Please see Reply to Comment A.2.

Changes in the text B.1: Line 286 and lines 293-302

**Comment B.2.** Please briefly describe your nutritional protocol for neoadjuvant therapy for locally advanced esophageal cancer. How many patients received chemotherapy, how many received chemoradiation. How was the type neoadjuvant treatment selected? Most importantly, did type of neoadjuvant therapy influence weight loss and surgical resection?

Reply B.2: We have added information about the nutritional protocol to the Methods section (Setting). Neoadjuvant treatment is selected by the multidisciplinary tumor board and is standardized to the patient's indications per the NCCN guidelines. The most common were paclitaxel, carboplatin, fluorouracil, epirubicin, oxaliplatin, and cisplatin. And the majority received radiation. None differed across intervention type to a statistically significant degree. Also, median weight loss was not different comparing each individual drug to patients not on that specific drug at any of the time points examined.

This said, any relationship between type of neoadjuvant therapy and weight loss or progression to surgery has, as a causal antecedent, the patient's cancer characteristics. For this reason, analyzing this information in relation to outcomes would be misleading. The tables correctly show outcomes in relation to the antecedent, i.e., cancer characteristics.

Changes in the text B.2: Lines 61-68.

**Comment B.3.** Pre-existing weight loss usually occurs before diagnosis as a number of patients present with a degree of weight loss. Why did you calculate TWL from diagnosis to index. It seems you are not accurately describing patients who lost weight prior to diagnosis.

Reply B.3: We regret that we were not clear that weight loss between the diagnosis to index date was a descriptive variable and not the outcome variable. The outcome variable was anchored to the moment when a physician would make the decision to intervene. Nearly all interventions were timed to the start of neoadjuvant therapy. We have moved baseline weight loss from Table 2 to Table 1.

Changes in the text B.3: Tables 1 and 2.

**Comment B.4.** A large number of patients did not go on to receive surgery. It seems that not all patients were treated as a neoadjuvant approach, but rather as definitive therapy. This should be clarified. What was the reason for no surgery in all patients?

Reply B.4: We appreciate this important comment. This information was obtained during chart review, which was performed for all J-tube and stent patients but only a random sample of 20 no-intervention patients. In the first paragraph of the Results section, we now clarify the percentage

of patients in each group that was chart reviewed who were definitive vs preoperative (72%-80%) and note no significant difference across groups ( $p=0.79$ ) In addition, we have added a sentence to the Discussion.

Changes in the text B.4: Lines 157-160 and 246-252.

**Comment B.5.** Why were only 20 patients with no procedure reviewed for complications?

Reply B.5: Study resources were limited, and patients without an intervention, by definition, cannot have an intervention-related complication. We now explain this in the methods section.

Changes in the text B.5: Lines 126-130.

**Comment B.6.** Cross over between groups is a major limitation - Patients who received their first J-tube or stent more than 10 days after starting adjuvant therapy were reclassified as receiving no prophylactic intervention. The manuscript could be improved by analyzing as an 'intention to treat' and 'as treated' analysis.

Reply B.6: The analyses we provide is an intention-to-treat analysis, as now stated explicitly in the methods section and in the title of Table 2. Most of the reinterventions were performed because of weight loss. For example, 35% of stent patients received a J-tube after the start of follow-up. We disagree that an as-treated analysis would be informative, second interventions were caused by excess weight loss or complications, the two study outcomes. Rather, we have added a sentence to the limitations.

Changes in the text B.6: Lines 87 and 208-213 and Table 2.

**Comment B.7.** Complications after intervention do not seem appropriate, I would not categorize pain as a complication. Again, where the no intervention group charts actually reviewed? What number of these patients had reflux or pneumonia during neoadjuvant therapy.

Reply B.7: With respect, we wish to retain pain because it was noted to be an important symptom leading to removal of the stent (a reintervention). Yes, 20 no-intervention charts were actually reviewed. We do not trust that recoding for reflux is complete and cannot report that. We performed additional analysis for pneumonia as a complication.

Changes in the text B.7: Lines 116-117, 122-133, and 186-187.

**Comment B.8.** Why was follow up included to 120 and 180 days, this would be postoperative for patients who made it to surgery and add complexity to the analysis. CROSS regimen is usually 5 weeks, followed by surgery 4-6 weeks after completion of CRT. Since postoperative time period was included, what operation was performed, what was the number of complications after surgery. This would significantly impact weight recovery and is not analyzed.

Reply B.8: Per our Kaplan-Meier approach, follow-up ended on the date of surgery, as explained in the Methods.

Changes in the text B.8: Line 135; footnotes added to Table 2 and Figure 1.

**Comment B.9.** How were jejunostomy tubes placed – laparoscopic, IR, endoscopic? A brief description would be helpful.

Reply B.9: We have added a new section, Setting, to the Methods section. Ninety percent were laparoscopic and 10% open.

Changes in the text B.9: Lines 67-68.

**Comment B.10.** The abstract of manuscript would be improved by adding a sentence to conclusion about what the authors recommend for perioperative nutrition for esophageal cancer patients based on their results.

Reply B.10: Thank you for this good suggestion, we have added a sentence to the conclusion.

Changes in the text B.10: Lines 27-29

**Comment B.11.** Discussion section is poorly written. Their summary of previous literature and comparison to manuscript results should be improved. Limitations should be discussed towards the end of the discussion.

Reply B.11: We have improved the summary of the previous literature and comparison to results. The Limitations discussion has been moved down.

Changes in the text B.11: Lines 232-252

**Comment B.12.** The number of references is limited should be increased when revising the discussion section.

Reply B.12: We have increased the number of references.

Changes in the text B.12: We have added references 8-10 (not tracked because it is difficult to follow in track changes).

## **Reviewer C**

Very nice observational study examining the effectiveness and associated drawbacks of three different approaches for nutritional support for patients beginning neoadjuvant therapy prior to planned esophageal resection for stage II and III esophageal cancer. Though selection bias is inevitable, this is a nice study within the controlled confines of a large Healthcare system where variations within each group are likely minimized.

**Comment C.1:** The only minor issues I see is that patients who underwent G-tube were appropriately excluded, yet they appear in Figure 1. I would remove the G-tube group from Figure 1.

Reply C.1: We regret that the wrong figure had been uploaded. We now provide the correct figure.

Changes in the text C.1: Figure 1.

**Comment C.2:** Also, were all of the J-tubes done the same way? Open or laparoscopic? If different approaches were used, were there any differences in complication rates within the groups?

Reply C.2: Of the 39 J-tubes, 4 were open and 35 were lap. We now provide this information on in the text. With only 4 open procedures, it was not possible for us to make a comparison.

Changes in the text C.2: Lines 66-68 and 157-160.