

Peer Review File

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Reviewer A (Review/Answer)

1. It appears that the endo-vac remains in place the entire time stent is in place. Do patients get discharged home? Does the suction tubing come out through one of the nares? Is there a portable suction device for this? How does this strategy not cause undue pressure on the esophagus and neo-conduit thus risking ischemia and conduit loss - can the authors explain that?

-Answer: We thank the reviewer for the comment. Although there are portable suction devices, we have not used them in this series as all therapies were performed with central aspiration in the room. All patients were discharged without EndoVac. The pressure was maintained within a range of 100-120 mmHg that has been shown not to cause ischemia but rather improve healing as explained in the discussion section. On the other hand, daily flushing and endoscopic control every 48hs to rewash if needed allows to prevent decubitus lesions. We have expanded the comment on this on the manuscript for clarification.

2. The n of 6 in the study is extremely small to establish any conclusive results. Larger studies are warranted to demonstrate efficacy. How many stents were exchanged? And did any of the stents migrate? Were any anti-migration strategies used?

-Answer: We agree with the reviewer that 6 is a small number to draw definitive conclusions. However, due to the rareness and complexity of these cases, we believe this small series serves as a proof of concept to inspire larger studies on the field. There was no need to replace stents. Stent migration was controlled through chest X-ray, and if they were found to be displaced, an endoscopy was performed to reposition it (2 cases). This was not clarified in the original manuscript and we have added the migration rate to the text.

3. How many of the patients required stent, all of them? There is a discrepancy where the authors state that FSEMS was removed routinely 8 wks after placement, yet under results, the time of FSEMS placement was 7 days with median time of defect closure of 19 days. How is that possible?

-Answer: We thank the reviewer for this relevant finding. In order to clarify, relay therapy includes both approaches (EVAC and Stent), therefore a stent was placed in all patients. 7 days is the mean postoperative time in which the FSEMS was placed. The mean time to closure of the defect was 19 days, and the time of removal of the stent was 4 weeks. We have noted that due to a typo, the original manuscript stated 8 weeks. We have corrected the text for clarification.

4. The postop stricture rate seemed high, albeit that may be b/c of small numbers. One would think that stents would provide a matrix for healing and therefore prevent post-leak stricture.

-Answer: We agree and share the reviewer's observation. The stricture occurred in the late postoperative period (<4 months) and not during the treatment with relay therapy. Unfortunately, the stricture rate is similar to that reported in the literature for patients with anastomotic leaks after minimally invasive esophagectomy. The inflammatory and scarring pathway triggered after a leak seems to be determinant for final healing at the anastomosis

site. Stents are not able to prevent stricture in the long term, which remains a limitation. All patients with strictures were treated with dilations in average of 2 sessions with full resolution of symptoms. We have added this information to the results section.

5. More details about the esophagectomy and anastomosis are needed re: technique (stapled vs. hand-sewn vs. hybrid)? I am assuming that all the anastomosis were intra-thoracic since they all underwent Ivor Lewis?

-Answer: All anastomoses were intrathoracic (Ivor-Lewis) and were hand-sewn (this was added to the text). The surgical technique is explained in detail in another paper dedicated to it in the same AOE issue.

6. How can we mitigate erosion with relay therapy? The risk of erosion into neighboring structures such as the airway and aorta seems extremely high esp if patient is intubated with a trach/ETT balloon in place. I would recommend that the readers use this RT strategy with extreme caution and judgment.

-Answer: We agree with the reviewer's concern about erosion. Due to this risk we never use stents as primary therapy for a leak. Erosion of neighboring structures was not a problem in our series. Our hypothesis to explain that finding is that EVAC promotes initial healing inducing tissue remodelling and deployment of scarred thick tissue. That tissue acts as a wall to neighboring structures when the stent is placed in relay fashion. However, it is strongly recommended to use these techniques in controlled environments and by surgical teams trained in the management of these patients.

7. Minor grammatical errors were noted. The last para (lines 260-261) needs to be re-worded.

-Answer: The last paragraph was modified (lines 260-261).

Reviewer B (Review/Answer)

1. - Please define the type of anastomotic leaks (you mention type II and III)

-Answer: The classification of Type of anastomotic leaks was added to the text.

2. Please clarify if time of detection of leak was 2 days after surgery. If so, this is highly unusual; did you have patients that had leaks later and decided against using this therapy? Such early leaks are typically a technical issue and more often than not require conduit takedown.

-Answer: The mean time of appearance of the leak was 2 days (2-7 days). In patients with late leaks (7 days) this approach (RT) was also used. We understand that the early presentation of leaks has usually been related with technical issues. We tend to disagree with that statement as modern tools and better care has triggered early detection of leaks with almost no symptoms. Moreover, leaks related to highly ischemic conduit are likely to start the process in the immediate PO regardless of the technique. In our series, preservation of the conduit was not a problem. In fact, early EVAC allowed preservation of the conduit that many times is taken down to relieve patients from sepsis. All leaks (early and late) could be treated effectively with RT.

3. What was the overall rate of leaks in the study period?

-Answer: The overall rate of leaks in the study period was 14.6% (6/41 patients).

4. What happened to the patient requiring surgery? Was that a failure of the therapy?

-Answer: The patient who required surgery was due to empyema, and a thoracoscopy decortication was needed. RT was also performed in this patient, shortening the times of sepsis, leak closure, and hospitalization compared to other therapies in the EAL management.

5. You mention that all patients required dilations by 4 months, but on 2/6 had a stricture at 6 months. Please be clear on the definition of strictures, I would categorize all of them as having one

-Answer: The paragraph was modified to clarify this concept: “Two strictures occurred in the follow-up at 6 months (33.3%). These patients experienced dysphagia four months after surgery that turned out in anastomotic strictures and required endoscopic dilatation (rule of three sessions every three weeks was performed).”

6. How would you recommend choosing “relay therapy” vs stenting or EVT?

-Answer: This is an interesting question raised by the reviewer. Initially per protocol EVAC is attempted when a leak is diagnosed and conservative therapy is considered. If EVAC alone rapidly resolves the leak and allows the patient oral feeding, stenting is not necessary. RT is recommended when longer periods of healing are expected. We discourage use of stents as first therapy due to risk of erosion. The outcomes with RT are encouraging compared to individual EVT and stenting therapies in our experience and the reported literature. Randomized prospective studies are needed to make a strong recommendation for this approach.