

## Response to Reviewers

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Incidence and Treatment of Mediastinal Leakage after Esophagectomy: Insights from the MuMeLe Study

We are grateful to all the reviewers for their detailed comments and helpful suggestions. We incorporated all their feedback as outlined in detail below. In addition, we highlighted the changes in yellow inside the manuscript.

### Query 1

*It is reported that the leakage rate is varying across the seven centers from 1.5% to 20%. Please provide the respective leakage rates of the high- and low-volume centers.*

We added the new Table 2 in the “Results” section (page 8, which provides exactly this information.

### Query 2

*The reference 32 is the same as the reference 15.*

We deleted reference 32 in the “References” section (now there are only 31 references). Moreover, we substituted the numbering (15 instead of 32) at page 14 where we refer to this work.

### Query 3

*44% surgery for mediastinal leaks seems a very high number, what endoscopic treatment is offered in the centers? Sponge therapy? Stents? Radiologic intervention?*

In our series, surgical treatment of ML was used more often than generally reported in the literature. We think that there may be two reasons for this divergence. First, Eso-SPONGE that is an effective treatment for several leaks, has become available in Italy only in 2018, and hence, it was not available at the time when patients were included in our study. Second, several leaks were diagnosed earlier than the timing reported in the literature, indicating a possible technical problem in the construction of the anastomosis. Therefore, redo surgery was used in a relatively high proportion of cases. We include this explanation in the “Discussion” section (page 14).

### Query 4

*How was the MIS approach performed? Only purely thoracoscopic? Robotic assisted?*

As reported in the subsection “Patients and Surgical Procedures” (page 7) there were different approaches according to different centers: minimally invasive techniques were routinely used in four surgical centers, whereas robotic surgery was a routine procedure in one center. In the same page, we added (highlighted in yellow) more detailed information on the differences across centers and procedures.

### Query 5

*Also, learning curve numbers for each procedure per center would be useful for all the related results to be of more value.*

Minimally invasive surgery was routinely used in four centers and all four of them have a large experience with hybrid technique, whereas the number of totally minimally invasive Ivor Lewis were

still in the learning curve in all centers with 1 center including more than 60 cases. We added this information on page 7.

#### **Query 6**

*I am wondering if there was a correlation between the hospital with high incidence of leakage and that with high incidence of minimally invasive surgery. If so, there was a strong bias of the study. Could the authors comment on whether this hospital correlation existed or not?*

The incidence of ML was higher among patients undergoing MIIL: a high incidence of ML was therefore reported in the center with the highest number of MIIL. As well-known, there is a problem with the learning curve for this surgical procedure, mainly related to the anastomotic technique. This may also explain the fact that in our series leaks were diagnosed earlier than usually reported in the literature, indicating the presence of a technical problem in the anastomotic technique. We add this discussion on page 12.

We do not think that this leads to a bias in our findings. In fact, what we find in our series is consistent with what reported in the literature, which indicates a trend toward a more diffuse use of minimally invasive technique for esophagectomy, even if the number of anastomotic complications for this operation is higher, at least until the learning curve ends.

#### **Query 7**

*The rate of removal of the gastric tube with formation of the stoma was relatively higher than other studies. Could the authors comment on it?*

Removal of the gastric tube becomes an important option in the case of extensive necrosis of the gastric tube or when a patient's general conditions are critical. In our experience the rate of this surgical option was higher than that reported by others but helped to maintain a relatively low mortality rate, which is clearly the most important goal.

#### **Query 8**

*The authors used the description "aggressive" as their conclusion. Did "aggressive" mean "surgical"? This is very subjective word.*

When facing a patient who develops a ML, it is important to act swiftly in the diagnosis of septic and ischemic complications. This leads to the decision of actively treating the complication either endoscopically or surgically. In our experience and reported series, the number of patients receiving either endoscopic or surgical treatment was high and this approach has been classified as "aggressive". Still the mortality rate (again, the key variable) was low and actually lower than the ones reported in the literature.

To avoid confusion, though, in the revised manuscript we avoid using the adjective "aggressive" and we explain what we mean in a clearer way.

#### **Query 9**

*Although the surgical intervention was different among the institutes, some criteria for surgical intervention must be existed. Please describe the indication of surgical intervention.*

Surgery was generally the preferred treatment for very early leaks when a redo anastomosis was considered the elective treatment before septic signs would appear. Other conditions where surgery was considered indicated were the presence of ischemic tissue at the anastomotic site or a septic patients with non-contained leaks. Lastly, surgery was used when conservative treatment failed. We added this clarifying paragraph in the "Results" section (page 10).

#### **Query 10**

*There were questions about some numbers in the Tables. We rechecked them completely.*