

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 41632

Title: Incidence and treatment of mediastinal leakage after esophagectomy: Insights from the multicenter study on mediastinal leaks study

Reviewer's code: 03270518

Reviewer's country: Italy

Science editor: Ruo-Yu Ma

Date sent for review: 2018-10-22

Date reviewed: 2018-10-31

Review time: 8 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The reference 32 is the same as the reference 15.

INITIAL REVIEW OF THE MANUSCRIPT



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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 41632

Title: Incidence and treatment of mediastinal leakage after esophagectomy: Insights from the multicenter study on mediastinal leaks study

Reviewer's code: 00058104

Reviewer's country: Greece

Science editor: Ruo-Yu Ma

Date sent for review: 2018-11-15

Date reviewed: 2018-11-17

Review time: 2 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

To the authors: The manuscript entitled "Incidence and Treatment of Mediastinal Leakage after Esophagectomy: Insights from the MuMeLe Study" is retrospective study that aims to investigate the incidence and treatment of post-esophagectomy MLs.



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Authors present the findings of their indeed extended work. However, this manuscript needs improvement in almost all of its sections. Please, find below a list of comments:

Comments Methodology: - The methodology is not well presented. There is alot of information that belongs to the results section. A better structure of the methods sections is needed. - Waiver of study consent approved by the IRB is presented to be somehow justified due to the clinical surgical patients' consent. Data capture and use for study reasons has nothing to do with the clinical consent and data management. This is of outmost importance for the authors to understand!!! - There is no need to mention an author's name in the text. Results: - Please, do not dublicate text and tables information. - Legends are used to provide expenations not to provide additional data. - Results presentation need a critical presentation improvement. The reader is hard to follow the information provided on the text and in the tables. - Numbers of each teqnique per participating center should be provided. Also, learning curve numbers for each procedure per center would be useful for all the related results to be of more value. Discussion: - Study limitations should be explained. - The experience of each participating center on each of techniques studied should discussed.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 41632

Title: Incidence and treatment of mediastinal leakage after esophagectomy: Insights from the multicenter study on mediastinal leaks study

Reviewer's code: 00253974

Reviewer's country: Germany

Science editor: Ruo-Yu Ma

Date sent for review: 2018-11-15

Date reviewed: 2018-11-22

Review time: 7 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input checked="" type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
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<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The manuscript is well structured. The authors discuss the existing literature in detail. The attached tables and figures are supporting the contents and are giving a good overview about the included studies. In summary, I am in principle very positive with



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regard to this study. Nevertheless, there are shortcomings. Minor revisions: 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. 2.) The 30- and 90-day leak-related mortality rates described in the abstract, is compared to the passage in the results part, not clearly formulated.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 41632

Title: Incidence and treatment of mediastinal leakage after esophagectomy: Insights from the multicenter study on mediastinal leaks study

Reviewer's code: 03565143

Reviewer's country: Japan

Science editor: Ruo-Yu Ma

Date sent for review: 2018-11-15

Date reviewed: 2018-11-26

Review time: 11 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors conducted the retrospective study using 501 patients underwent esophagectomy with intrathoracic esophagogastric anastomosis. They analyzed the anastomotic leakage: mediastinal leakage (ML) and its related mortality. They found that

the surgical approach significantly influenced the occurrence of ML. The incidence of ML was highest in totally minimally invasive esophagectomy (TMIE). The 30- and 90-day overall mortality rates were 1.4% and 3.2%, respectively; the 30- and 90-day leak-related mortality rates were 5.1% and 10.2%, respectively. In their study, surgery was performed in 44.1 % of ML cases. Furthermore, removal of the gastric tube was necessary in 13.6% of the ML cases. They concluded that the early aggressive treatment of severe leaks is mandatory to limit related mortality. This study is well written and interesting. However, there are several issues in this manuscript that should be further described. Furthermore, there were so many mistakes in the Tables that should be corrected. Comments; 1. 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? 2. 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? 3. The authors used the description “aggressive” as their conclusion. Did “aggressive” mean “surgical”? This is very subjective word. 4. Although the surgical intervention was different among the institutes, some criteria for surgical intervention must be existed. Please describe the indication of surgical intervention. 5. In Table 1, total patient number was 501, however, in some factors, sum of the numbers was different. Please check the number correctly. 6. In Table 1, location of the tumor should be included. 7. In Table 2, there was p value at the bottom of the Table. What did the authors compare? Please describe the Table more intelligible. 8. In Table2, some footnote of the Table should be described in the manuscript, instead of the footnote of the Table, e.g. “Leaks were diagnosed as follows: 38 radiologically, 18 endoscopically, 2 clinically, and 1 surgically”. 9. In Table3, some footnote of the Table should be described in the manuscript, instead of the footnote of the Table. Footnote should be mainly for the



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explanation of the abbreviations in the Table. 10. In the Table 4, number of primary therapy should be reflected as the number of total leaks. Please check the number correctly.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 41632

Title: Incidence and treatment of mediastinal leakage after esophagectomy: Insights from the multicenter study on mediastinal leaks study

Reviewer's code: 03259368

Reviewer's country: Germany

Science editor: Ruo-Yu Ma

Date sent for review: 2018-11-15

Date reviewed: 2018-11-26

Review time: 11 Days

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SPECIFIC COMMENTS TO AUTHORS

The authors present an interesting study and should be commended for their work. Fumagalli et al aim to assess the incidence, predictive factors, treatment, and associated mortality rate of mediastinal leakage (ML) after esophagectomy. These multicenter

studies are very work-intensive and need a lot of time. Their study adds to the literature. ML was classified according to the newest ECCG classification. The topic is very interesting and important. Nevertheless, I do not agree with the conclusion of the paper, even if the included data suggest this conclusion for the Italian centers. Interestingly, ML was significantly influenced by surgical approach: „The surgical approach significantly influenced the occurrence of ML: the proportion of leakage was 10.5% and 9% after open and hybrid esophagectomy (HE), respectively, and doubled (20%) after totally minimally invasive esophagectomy (TMIE) ($p=0.016$) „ I am sure this is due to compromises performing the anastomosis during MIS esophagectomy in the different centers. In our super high volume center for upper GI cancer in continental Europe ($n>200$), we perform the anastomosis in the same way for MIS and hybrid cases with a circular stapled anastomosis. Mortality was in the range reported in literature, so I guess performance in the reported collective is good. 44% surgery in ML seems a very high number, what endoscopic treatment is offered in the centers? Sponge therapy? Stents? Radiologic intervention? How was the MIS approach performed? Only purely thoracoscopic? Robotic assisted? It becomes clear that the main lack of the study is the not existing standardization of surgery and complication management in the different centers. Therefore this study in my mind does not compare the different techniques, but the experience of 7 different Italian centers. In addition, state of the art endoscopic technology (ESOSPONGE) for treatment of esophageal leaks was not offered to the patients in this study. (..because Eso-SPONGE is not yet commercially available in Italy ..) I suggest modifying the conclusion and add this very last paragraph to the paper: “This study shows the high variation in surgical technique and complication management in the included centers. More standardization of anastomotic techniques and endoscopic complication management is needed to draw significant conclusions and understand the origin of ML after esophagectomy and to improve outcomes.”



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