

Dear Science Editor, dear Ze-Mao Gong,

Thank you for the opportunity to revise our manuscript, Synthetic versus biologic mesh for repair and prevention of parastomal hernia. We appreciate the careful review and constructive suggestions.

Following this letter are the editor and reviewer comments with our responses, including how and where the text was modified. Changes made in the manuscript are marked. The revision has been performed in consultations with all coauthors, and each author has given approval to the final form of this revision.

Sincerely,

Loes Knaapen, MD

Reviewer 1:

- 1a. p.9 Methods: Following 'Intervention' prophylactic mesh should be added
- 1b. p.11 Results: Prophylactic mesh repair? Should be re-phrased as 'prophylactic mesh placement'
- 1c. p.15 Results: Keyhole was used in eight of the studies, not seven.

Thank you for these comments. We have changed the text according to the comments in the manuscript.

- 2. p.12 Results: Synthetic mesh repair, second sentence does not make sense or is easily misunderstood.

First, the authors cite more than one prospective study in the list of references. Second, the study mentioned (Pastor, ref 34) recruited 12 and 13 patients, respectively, not 669 patients.

Apparently, this part was not clearly stated.

Concerning all synthetic mesh repair and biologic mesh repair included in this systematic review, there was only 1 prospective study of Pastor EM, et al (ref 26).

We revised the sentence into at page 12 into:

'One of the 21 studies was a prospective trial that recruited 12 patients with synthetic mesh repair and 13 control patients without mesh repair. The other 20 studies had a combined enrolment of 669 patients with synthetic mesh repair.'

3. p.20 Discussion: 'Occurrence of seroma formation....all ePTFE-repairs... [5, 15, 30]. Ref 5 used, however, a polypropylene-based mesh covered by e-PTFE.

We thank the reviewer for this comment. We changed the text in Table 3 into Polypropylene based mesh covered with ePTFE. In the discussion seroma formation was related to laparoscopic repairs not specifying the type of mesh used.

4. p.22 Discussion: The authors state that only one type of mesh was used for repair, failing to state what mesh, but it is supposedly an e-PTFE mesh. In two studies, however, polypropylene-based mesh was used (PP+ePTFE, ref 5 and PP+PVDF, ref 7) and in the third study Polyester and PP+PTFE was also used (ref 26).

Thank you for this remark. This is indeed confusing. We decided to completely delete the statement 'With respect to laparoscopic parastomal repair all studies were performed with one type of synthetic mesh. The reason for that remains unexplained as there are different types of mesh available for intra-abdominal use' because this did not add much to this part of the discussion

5. p.24 Discussion: The authors state that Sugarbaker is superior to Keyhole, the same conclusion as drawn by Hansson [ref 11] and Asif [ref 17]. Looking at Figure 5 in the paper of the authors and Figure 6 in the paper of Hansson (ref 11, p. 691) it appears that all failures using the Keyhole technique are related to the use of an e-PTFE-mesh [2,15,17,26,34]. Consequently, the conclusion is recommended to be revised to: The Keyhole technique should not be used with an ePTFE-mesh. The Keyhole technique using a polypropylene-based mesh worked well in one of the largest prospective study of consecutive patients (ref 5), and apparently also in 5 studies of open surgery as reported in the present paper.

Thank you for this comment. We agree with the reviewer and revised the text in accordance to what is suggested in the clinical implications paragraph: 'When performing laparoscopic repair, the Keyhole technique should be abandoned in favor of the Sugarbaker technique when using an ePTFE-mesh because of much higher recurrence rates. As show by Wara et al. the Keyhole technique can be considered when using a polypropylene-based mesh or with open parastomal keyhole hernia repair.'

6. Number of reference should be added to each author in the tables and figures.

We have added the reference to each author.

7. Table 1: Head second column: add ...of patients

The 'No' in this table referred to the identification number of the study as given by the author. As mentioned below, we decided that the value of this number in an already complex table is not contributory. Number of patients is mentioned in Table 3.

8. Table 3:

8a First column head: No of what?

Identification number of the study as given by the author. We agree that the value of this number in an already complex table is not contributory, when the reference number is added. We deleted the column from all the tables.

8b Second column head: Re-phrase 'without lost to f-up', f ex 'completed follow-up'.

8c Fourth column: Ref 5 (Wara) used a PP-based mesh covered with e-PTFE.

8d Column head: Add 'Recurrence of parastomal hernia

All above suggestions have been implemented in the manuscript.

9. Figure 6: The title should be re-phrased to Prophylactic mesh placement

*We thank the reviewer for this comment. 'We changed prophylactic mesh repair in to prophylactic mesh **placement** the titles of both Figure 6 and Table 6 as suggested*

10. The brackets with number of reference are in the text sometimes placed after the period in the next sentence, in the middle of the sentence or the numbers are lacking.

Thank you for your observation. We have reviewed the references more carefully and adjusted them if needed.

11. p.7 Introduction: ...focus on hernia recurrence In the absence of hard data in the literature the review contributes to increased knowledge of parastomal hernia.

*Thank you for this comment. We agree and have added it to the last sentence of the introduction section: **'With the absence of rigorous data focused on hernia recurrence in the literature, this review contributes to the increased understanding of parastomal hernias.'***

Reviewer 2:

1. The manuscript is very comprehensive, but the combination of parastomal hernia repair and prophylaxis might make it too much as a whole. Especially given the fact that seven meta-analyses on prophylactic mesh placement have been published in the last 2 years, it could be considered to focus on treatment only.

Unfortunately, at the time the manuscript was written others were also inspired to write a systematic review about prophylactic placement of mesh at initial stoma placement. However, when we focus on hernia occurrence and recurrence in the absence of hard data in the literature the review contributes to give a complete overview of this topic and increases knowledge of parastomal hernia.

2. p.6 Introduction: In the Methods section, the paragraphs on the surgical techniques seem a bit odd. First the selection is addressed, then surgical technique, followed by data extraction. The authors should consider moving them to the introduction section.

We agree with the reviewer and moved the whole paragraph to the introduction section with minor changes to the text.

3. Considering the outcome and follow-up, two questions rise. They are briefly mentioned in the discussion, but might need some more attention

3a. p.23 Discussion: Some of the studies have a follow-up period under 12 months. It might be considered to have a minimum period of at least 12 months.

*Follow-up time does have a strong impact on the outcome. However as there was already little literature available concerning our topic, we decided to abandon the 12 month period and decided to mention it in the discussion as follows also to point out that the follow-up time of the current evidence is indeed worrying.: **'Reported follow-up periods within and between studies varied from 7 months to 51 months. As recurrence occurs mostly in the first years after operation a minimum follow up of 12 months seems appropriate.'***

3b. p.23 Discussion: No details are provided on the method of PSH diagnosis: is it physical examination, US, or CT? This can cause considerable differences.

We decided not to include this in our review because the modality of diagnosis was often not or not clearly stated in the studies. We addressed the lack of PSH diagnosis in the discussion section at page 19 and page 23.

4. p.21 Discussion: When discussing prophylactic mesh placement, some attention could be paid to non-mesh prophylaxis like lateral placement (Stephenson et al. Colorectal Disease 2010) or extraperitoneal colostomy (Kroese et al. Disease of the Colon & Rectum 2016).

*Thank you for this suggestion, we added the following statement to the discussion at page 21: **'Other non-mesh prophylactic measures can be considered, such as lateral rectus abdominis positioned or extraperitoneal positioned stomas.'***

5. p.24-25 Discussion: The statements that prophylactic mesh placement should not be used routinely are not based on the data (in contrary), but on personal opinion. To my opinion, the final statement should therefore be a bit more reserved.

*We agree with the reviewer and have rewritten the statement; **'Prophylactic mesh reinforcement during stoma formation significantly reduces parastomal hernia occurrence regardless of mesh type. Yet, a significant number of patients will develop asymptomatic parastomal hernia and there are no data on long term effects of preventive mesh placement. Therefore, it is essential to select the right patient for whom prophylactic reinforcement is mandatory.'***

6. Table 6 title: 'prophylactic mesh repair', this seems odd. Change it to 'prophylactic mesh placement'.

'We changed the title of table 6 as suggested: 'Table 6 Study characteristics and outcome of prophylactic mesh placement of parastomal hernia.'