ANSWERING REVIEWERS

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc).

Title: Risk factors associated with missed colorectal flat adenoma: A multicenter retrospective tandem colonoscopy study

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ESPS Manuscript NO: 8431

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Thank you very much for your letter and advice. We have revised the manuscript, and would like to re-submit it for your consideration. We have addressed the comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript. In addition, point-by-point responses are listed below this letter.

This manuscript has been edited and proofread by Medjaden Bioscience Limited.

We hope that the revised manuscript is acceptable for publication in the journal.

We look forward to hearing from you soon.

With best wishes,

Yours sincerely,

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Response to reviewer #1:

This is an interesting paper on the risk factors associated with missed flat adenomas, which provides a contribution to the current knowledge of this topic. There are some flaws, most of them are minor.

Answer: Thank you for your positive and encouraging remark.

ABSTRACT

Methods: The authors should specify what they clearly state in the Discussion, i.e. that that chromoscopy and high-definition colonoscopy have not been taken under consideration in the study, as this is an important limitation.

Answer: We have added a sentence to address this issue in the Abstract of the revised manuscript accordingly.

Results:

“2,093” not “2093”

Answer: The correction has been made in the revised manuscript accordingly.

INTRODUCTION Line 21: better “use” than “application”

Answer: The correction has been made in the revised manuscript accordingly (Page 4, Line 22).

METHODS

Lines 6-9: there is no need to mention the Institutions here, first because they are already mentioned below the title and the authors, second because they are mentioned a few lines below,

in the ethic committee list. Delete them please, otherwise there would be a repetition.

Answer: The Institutions have been deleted in the revised manuscript accordingly (Page 5, Line 14).

Selection criteria

Line 5: “under ..” better “with…”

Answer: The change has been made in the revised manuscript accordingly (Page 6, Line 2).

Line 10: “normal colonoscopy”. I presume that the 100 colonoscopies required were total colonoscopies. If so, add “total”.

Answer: “total” has been added in the revised manuscript accordingly (Page 6, Line 7).

Line 16: better “partial large bowel resection” than “intestinal segment resection of the colon” for two reasons: b) according to a correct surgical terminology, both right and left hemicolectomies are not “segmental” resections c) anterior resection of the rectum of course is not a resection of the “colon”.

Answer: Thank you for your insightful suggestion. The change has been made in the revised manuscript accordingly (Page6, Line 13).

Colonoscopy and imaging

Line 1: better to avoid the term “colonic lavage”, as it can be interpreted as “hydrocolonic lavage” a procedure also used (less often) as pre-colonoscopy preparation (Pizzetti, Colorect Dis 2006). Better to say “Large bowel preparation (or cleansing) was performed using…”.

Answer: Thank you for your thoughtful suggestion. The change has been made in the revised manuscript accordingly (Page6, Line16).

Line 3: better “first” than “while primarily”. Line 5: “carried out”, not “done”.

Answer: The change has been made in the revised manuscript accordingly (Page 6, Line 18，and Page 6, Line 20).

Study endpoints

Line 21: “normal”: please see above the comment on line 10 of the “Selection criteria”.

Answer: The change has been made in the revised manuscript accordingly (Page8, Line 10).

RESULTS

Lines 3 etc: “4,567” not “4567” etc Clinical and pathologic….

Answer: The change has been made in the revised manuscript accordingly (Page 10, Line 6).

Line 5: “size 10 mm”. Is that the size measured during colonoscopy or by the pathologist? Then, in the Discussion a few words should be said about the difference between these two measures, due to the retraction of the specimen once excised.

Answer: Thank you for your careful review and the useful suggestion. We apologize for the mistake in the description on the measurement of the adenoma size in the preparation of the original manuscript. In fact, the adenoma size was measured by the colonoscopist during the colonoscopy using the opening aperture of a biopsy forceps (6 mm as a cut-off value), or measuring the size of the adenoma after resection. Accordingly, we have corrected the

description and clarified the issue in the revised manuscript (Page 8, Lines 13-15).

DISCUSSION See above,

RESULTS, Clinical … Line 5 FIGURE 1

Line 1: “2,093” not “2093” etc

Answer: The change has been made in the revised manuscript accordingly (FIGURE 1, Line 12).

TABLE 2 “4,632” not “4632” etc

Answer: The change has been made in the revised manuscript accordingly (Page 29, Line 2-20).

TABLE 3 Better “Previous surgery” than “Surgical history”

Answer: The change has been made in the revised manuscript accordingly (Page 31, Line 17).

TABLES P values might be better indicated either with P< … when statistically significant with P= … when not statistically significant or all with P=…

Answer: The changes have been made in the revised manuscript accordingly; all with *P*=… except for *P*<0.001.

FIGURE 1 4,567 1,473 2,093

Answer: The changes have been made in the revised manuscript accordingly (FIGURE 1, Line 2, 4, 13).

Responses to reviewer #2:

First of all, congratulations for your job! I think the design of the study was interesting. It was not clear if the use of chromoendoscopy with indigo carmine was done in all second look procedures in the description of methods and in the results.

Answer: Thanks for your congratulations. The indigo staining was done only in cases with areas suspicious of adenoma, which has been clarified in the Methods section of the revised manuscript accordingly (Page 6, Line21-24).

I did not found on the paper the method of endoscopic resection of flat adenomas: endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).

Answer: Either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) was carried out in this study, which has been added in the Methods section of the revised manuscript accordingly (Page 7, Line 1-2).

I neither found the endoscopic morphologic classification of flat adenomas that was described in the methods but not in the results. These aspects are important in a matter to predict post resection recurrence.

Answer: Thank you very much for your careful review and insightful suggestion, which we agree and accept. Accordingly, we have briefly presented the results on the two types of flat adenoma (*i.e.* flat elevated and flat depressed) in the Results section (Page11, Line 5-12). Of the 916 adenomas, 906 (98.9%) were classified as flat elevated and 10 (1.1%) flat depressed. The information on these two types of adenomas is briefly presented in the main text (Page 37, Lines 1-18) and Supplementary Table 1 of the revised manuscript.

In addition, we have added a few sentences in in the Discussion section of the revised manuscript

to address the possible association between the endoscopic morphologic classification and high-grade dysplasia (Page 16, Lines 8-15) and the importance in predating post resection recurrence (Page 19, Lines 6-11).