Dear Editor,

Thank you so much for preliminary acceptance and opportunity to answer the reviewer comments. Please find answers to all the comments below. We have uploaded the **IRB Approval, Biostatistics Review Certificate, Copyrights agreement forms, Audio Core tip and Conflicts of Interest form**. As this is retrospective study with chart review a patient consent is waived by IRB and not required.

We have made few minor changes in the manuscript as follows:

1. The **title of the study** has been modified as: Colon Mucosal Neoplasia Referred for Endoscopic Mucosal Resection: Recurrence of Adenomas and Prediction of Submucosal Invasion

2. , **In Table 1, 2 and 3** we have **regrouped the Paris classification** for better understanding of the readers. In accordance, we have updated the tables. All the changes in the manuscript and tables have been highlighted in yellow.

3. I am unable to make changes to the ORCID ID's. Below are corrected and confirmed ID's:

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4. Conflicts of Interest form has been updated and uploaded.

Please find answers to reviewer comments below:

REVIEWER 1:

1. The manuscript could be published if the conception of "recurrence rate "was modify them for clarity. It is hard to accept the conception that a benign polyp "relapse "after only 4 months of resection

   A. In our study, 354 lesions (70%) were examined at surveillance colonoscopy (SC) at 4-6 months interval. At initial endoscopic resection, lesion site was carefully examined for any residual abnormal tissue and resection was deemed complete only when no obvious abnormal residual tissue was noted, hence the term recurrence is used. Although the reviewer has very a valid point about relapse of benign lesions at 4-6 months follow up is unlikely but this is ongoing dilemma in research studies on endoscopic colon

polyp resection. It is still possible that there was residual abnormal tissue in spite of considering a complete resection at initial endoscopy but in literature term "recurrence/residual" is used complimentary and synonymously at least for now until future studies are better able to differentiate these terms.

2. EMR and ESD are two common endoscopic surgery for colonic polyps. EMR is of simple procedures and short time consuming. However, several pieces resections are required for large lesions, which is easy to result in residual lesions or called uncomplete resection (just as reported in this paper when the lesions are larger than 4cm). In contrast, ESD offers en bloc resection of larger flat or sessile lesions though it is difficult to operate and time-consuming.

   A. We do agree with reviewer that EMR and ESD are procedures with each having its own pros and cons for removal of larger colorectal lesions. We appreciate reviewer's comments.

REVIEWER 2:

1. The authors defined recurrence/residual as histological confirmation of adenoma at 4-6 months (SC), whereas, recurrence and early recurrence is mentioned separately in the manuscript. How to distinguish recurrence and residual? And what is defined as "early recurrence"? Whether the residual rate was calculated?

A. In the manuscript the terms (early recurrence and recurrence) have been corrected to recurrence only. At initial endoscopic resection, lesion site was carefully examined for any residual abnormal tissue and resection was deemed complete only when no obvious abnormal residual tissue was noted, hence the term recurrence is used. Although the reviewer has very a valid point about relapse of benign lesions at 4-6 months follow up is unlikely but this is ongoing dilemma in research studies on endoscopic colon polyp resection. It is still possible that there was residual abnormal tissue in spite of considering a complete resection at initial endoscopy but in literature term "recurrence/residual" is used complimentary and synonymously at least for now until future studies are better able to differentiate these terms.

2. In the part of Introduction, "Until recently, large colon polyps have been treated most commonly with either open or laparoscopic surgical resection" , in the part of Discussion, come to the conclusion that "EMR of larger polyps is a safe and viable alternative to surgery", however, without any data presentation of surgery, which makes the argument less persuasive.

A. Thank you for the kind comments. These arguments were stated based on fact, endoscopic procedures being minimally invasive procedures as compared to open or laparoscopic surgeries (ref 6 and 16). Though we agree with reviewer that unless there is comparative data it may be less persuasive but there is good

separate data available on both surgery and endoscopy technique to support the notion as in this study that showed that almost 99 % of larger polyps were successfully removed by endoscopic procedure without any major adverse events.

3. In the part of Results, "At surveillance colonoscopy (SC), 354 post-EMR scars were examined, and the remaining did not undergo (SC) due to carcinoma, incomplete or partial resection of adenoma at initial EMR, no follow-up available, or other reason." To my confusion, patients with carcinoma and incomplete or partial resection of adenoma theoretically require intensive surveillance, why didn't they undergo surveillance colonoscopy? What's more, patients with incomplete or partial resection of adenoma may be at high risk of recurrence, the authors calculated the adenoma recurrence rate of 21.8% that excluded those patients, evidently the reality of the rate is doubtable.

   A. Thank you for the comment. We do agree that patients with carcinoma, incomplete or partial resection of adenoma at initial EMR needed either close follow up or other intervention. All these patients with carcinoma or incomplete resection were referred for surgical resection and did not undergo regular surveillance as would be after EMR. After surgery they followed with their respective Gastroenterologists for follow up screening and surveillance.

REVIEWER 3:

1. A clear definition of cancer and SMI should be added: authors describe the presence of 29 cancers and 23 SMI. Are the 23 cases with SMI included in the 29 cancers? If this is the case, which are the characteristics of the remaining 6 cancers (muscular invasions?); if they represent 2 different groups, which are the criteria to define one group cancer and the other SMI

   A. Thank you for the comment. Yes, these 23 were out of these 29 patients. Rest of the six cases, were reported to be intramucosal cancers without submucosal invasion. This statement has been added to the manuscript and has been highlighted yellow.

2. Regarding the factors associated to SMI at univariate analysis Kudo pit pattern results to be significant; it should be, however, better clarified which Kudo pattern is associated to the risk; in the previous sentence, authors state that the majority of SMI have a Kudo IIIL pattern; this sentence could be misleading considering that the same rate is present also in patients without SMI.

   A. Thank you for the comment. Manuscript has been reviewed by biostatisian. The SMI was more prevalent with Kudo pit pattern (IIIL+IV and V). This has been corrected in the Table 3 and in the manuscript and highlighted yellow.

3. In table 3, it is reported that the Kudo 5 pattern results to be significantly associated to SMI using as reference the other patterns; however, in brackets, also IIIL, IV and Vn are reported. What does it mean?

   A. Thank you for the comment. Manuscript has been reviewed by biostatisian. The SMI was more prevalent with Kudo pit pattern (IIIL+IV and V). This has been corrected in the Table 3 and in the manuscript and highlighted yellow. The other lesions (except Kudo pit pattern IIIL+IV and V) were taken as reference mentioned in the table 3

4. In the chapter: "Multiple logistic regression analysis of risk factors for recurrence of adenomas" in the fourth line the value regarding the OR for lesion size 21-30 mm is lacking.

   A. Values have been added and highlighted in yellow

5. In table 1, if you consider the median you should report the range and not the SD; otherwise, you should report the mean (if applicable)

A. Table has been modified to show Median and Range. (Highlighted in yellow)

REVIEWER 4

1. Abstract: it is not structured according to Editorial guidelines (i. e. Background and aim is a single section); the first sentence of Conclusions, "This is one of the largest single-center studies reporting..." seems to be an introductive/aiming aspect more than a conclusion.

   A. Abstract has been modified in accordance with Editorial guidelines. Background has been added. The sentence "This is one of the largest single-center studies reporting ..." has been shifted to background. All changes are highlighted in yellow.

2. Core tip is absent.

   A. Core tip has been added and highlighted in yellow.

3. Introduction: the aim of the study is lacking.

   A. Aim has been added and highlighted.

4. Institutional Review Board approval of this study and informed consent need to be better detailed.

   A. IRB approval will be uploaded. As this is retrospective study with chart review a patient consent is waived by IRB and not required.

5. For immediate follow-up, we telephoned patients within a week and recorded any adverse events": a week seems to be a period too long to detect immediate complications "Perforation that develops after patients are discharged from the hospital, and patients presenting again to the hospital with abdominal pain, distension and signs/symptoms of peritonitis."; please detail.

   A. Patients after the procedure were observed for few hours and discharged afterwards in the absence of any obvious immediate complications, patients were discharged on the same day with necessary instructions about post-EMR procedural care. For a regular follow-up as per our endoscopy unit protocol all the patients were contacted in order to note the complications that developed after the discharge to home in case patients presented to some other hospital.

6. Results: "cancer was found in 29 cases" and "submucosal invasion was found in 23 cases"; a spontaneous question is: does submucosal invasion define the presence of cancer? If yes, as well-known, how do Authors explain this discrepancy?

   A. Thank you for the comment. 29 patients were diagnosed with cancers and 23 of these patients had submucosal invasion. Rest of the six cases, were reported to be intramucosal cancers without submucosal invasion. As per our study it is true that all submucosal invasion lesions were cancerous lesions. Aim of the study was to

determine what endoscopic features could predict the submucosal invasions and not the histological nature.

7. Finally, is a follow up period of 4-6 months adequate to establish cancer healing?

   A. Thank you for the comment. All the benign polyps were followed up that's why follow up was done at 4-6 months as per current findings and guidelines based on published literature (Ref 16). All the malignant lesions were referred to colorectal surgery teams for further management and afterwards patients followed with primary gastroenterologists for surveillance.

Regards,

Mamoon Ur Rashid

Corresponding Author