

Format for ANSWERING REVIEWERS



March 31th, 2016

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: wjg-2015-00056968.doc).

Title: DEVELOPMENT AND VALIDATION OF A RISK SCORE FOR ADVANCED COLORECTAL ADENOMA RECURRENCE AFTER ENDOSCOPIC RESECTION

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 25212

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

Reviewer 1:

This is a good study, however some revisions are required: Patients All colonoscopies were performed under deep sedation: Please provide the type of sedation.

RE: We have specified that all colonoscopies were performed under sedation with Propofol monitored by an anesthesiologist.

Following cleansing of the bowel using a polyethylene glycol-electrolyte solution: Please provide the modality of cleansing (hours, diet).

RE: We have specified that bowel preparation was split between the evening before and the morning of the procedure.

The interventional endoscopic techniques adopted at our center has been described elsewhere (References 10,12,13): - the reference 10 (Facciorusso et al. Factors associated with recurrence of advanced colorectal adenoma after endoscopic resection. *Clinical Gastroenterology and Hepatology* 2016, in press.) should be removed because this is not online. - the reference 13 (Facciorusso et al. Echoendoscopic ethanol ablation of tumor combined to celiac plexus neurolysis improved pain control in a patient with pancreatic adenocarcinoma. *Endosc Ultrasound* 2015) should be removed because this is not pertinent with the paper.

RE: Reference 13 has been deleted. Reference 10 is online: "Facciorusso A, Di Maso M, Serviddio G, Vendemiale G, Spada C, Costamagna G, Muscatiello N. Factors Associated with Recurrence of Advanced Colorectal Adenoma after Endoscopic Resection. *Clin Gastroenterol Hepatol.* 2016 Mar 19. pii: S1542-3565(16)00273-1. doi: 10.1016/j.cgh.2016.03.017. [Epub ahead of print] PMID: 27005802"

Resection technique In 2015 the same group published a paper that compared the efficacy and safety of the submucosal polidocanol injection (306 cases), with epinephrine saline solution injection (306 cases) for endoscopic resection of LST and sessile colorectal lesions performed between January 2005 and July 2014 (reference 12 Facciorusso et al. Polidocanol injection decreases the bleeding rate after colon polypectomy: a propensity score analysis. *Gastrointest Endosc.* 2015). The study submitted to *World Journal of Gastroenterology* is a retrospective analysis of lesions resected between January 2004 and

December 2008. The cases performed between January 2005 and December 2008 with submucosal polidocanol injection were excluded? If these cases were included in the study, should be specifically written in the methods section (Resection technique) and in the results section.

RE: We have specified: *"This timespan corresponded to the period when polypectomy was performed conventionally at our center, before introducing a novel technique using polidocanol injection described in a recent paper published by our group"* In fact, in the aforementioned paper of our group (ref 12), patients were treated with conventional saline injection between 2005 and 2008 and with polidocanol injection from 2009 onwards. Therefore, in the current study we retrieved data of patients treated in the period when conventional saline injection was adopted at our Institution.

Follow up Please insert in the adverse events also the transmural burn syndrome and if this complication occurred, also the rates in the results section.

RE: No patient experienced transmural burn syndrome in our cohort. This data has been reported in the text.

Reviewer 2:

This manuscript by Facciorusso A et al. reported a development of a novel risk score tool for colorectal adenoma recurrence after EMR and investigated the validation with relatively large sample size. The scoring tool has a good performance for predicting the recurrence and is easily applicable at the bedside. This study design involves several limitations such as retrospective database-based study and regarding follow-up time, but the authors well discussed on these matters in the manuscript. This manuscript has a value for publication with taking into consideration of points mentioned below. Minor comment

All the 843 patients with resected ACA in the study period were performed follow-up colonoscopy in the institute? Actually, no patients were lost to follow-up or rejected the exam or died with diseases?

RE: We have now specified in Material and Methods that *"All 843 patients underwent follow-up colonoscopies at our Institution"*. In fact, as clearly stated in the text, complete follow-up data was an inclusion criteria to our study.

In "Follow up" of "Material and Methods", "homeostasis" is "hemostasis"?

RE: The typo has been now corrected according to reviewer's suggestion.

I recommend to incorporate the actual scoring not only in the Table 3, but in the main body, which makes readers to easily understand.

RE: We have now clearly described among the Results: *"As described in Table 3, patients were given 4 points in presence of HGD, whereas lesions > 15 mm and multiple ACAs determined 3 and 2 additional score points, respectively (Table 3)."*

In the statistical analysis, the factor of "type of resection (en block or piecemeal) was eliminated by its collinearity with other parameters. However, previous many studies reported that type of resection has a strong impact for adenoma recurrence. Considering the impact, the type of resection should be influenced in the risk scoring in some way?

RE: We decided to exclude the variable "type of resection" (piecemeal versus en bloc) from the statistical model due to its collinearity with lesion size and morphology and because it may constitute an operator-dependent parameter, thus representing a potential confounder in our objective model. In fact the decision whether performing piecemeal or en bloc resection is strictly dependent on the lesion size and morphology (being more likely in presence of greater sessile and/or flat lesions) and this would present an important problem of collinearity in our model (where collinearity in statistics indicates a phenomenon in which two or more predictor variables in a multiple regression model are highly correlated, meaning that one can be linearly predicted from the others with a substantial degree

of accuracy. In this situation coefficient estimates of the multiple regression may change erratically in response to small changes in the model or the data). Notably, one of the baseline assumptions underlying regression analysis in medical statistics is the absence of collinearity. This, in addition to the subjective nature of this variable (often dependent on the local expertise and the operator) represents in our opinion an important reason to exclude "type of resection" from the multivariate analysis and RPA. We think this is an important point not adequately addressed in previous papers (such as that by Seo et al) and we consider it a further strength in our analysis.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Facciorusso Antonio

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