September 22, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13105-review.doc).

Title: Clinical Usefulness of Endoscopic Ultrasonography for the Evaluation of Ulcerative Colitis-associated Tumors.

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Name of Journal: *World Journal of Gastroenterology*

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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
(1) Reviewer 1 suggestions : In this paper Kobayashi et al. evaluated the clinical usefulness of endoscopic ultrasonography (EUS) for diagnosis of the invasion depth of UC-associated tumors, and concluded that EUS provides a good estimation of the invasion depth of UC-associated tumors. This paper is well written and the content of the paper is interesting. However, the authors should address the following points.

1. As the authors mentioned, intestinal inflammation due to UC might lead to overestimation of the depth of invasion. Thus, the authors should show whether colonic inflammation due to UC was observed in each case of the study.

Response
We reviewed conventional endoscopic findings at the time of EUS for the 16 UC-associated tumors studied. Active inflammation of the surrounding intestinal mucosa was found in 7 UC-associated tumors. These lesions mainly showed mucosal redness, edema, and erosions, and there was no evidence of severe intestinal inflammation, such as deep ulcers or spontaneous bleeding. In the other 9 lesions, the mucosa around tumors was in a remission phase. These findings were added to the Methods section.

2. The authors should demonstrate the differences for evaluating the invasion depth on EUS between sporadic tumors and UC-associated tumors.

Response
The diagnostic criteria used to evaluate the invasion depth of UC-associated tumors by EUS in our

study were similar to those used for sporadic colorectal cancer. In our series, the invasion depth of all but 1 UC-associated tumor was correctly assessed by EUS. This finding suggests that the diagnostic criteria used to estimate the invasion depth of sporadic colorectal cancer by EUS can be used to some extent to evaluate UC-associated tumors. However, in the presence of severe active inflammation or fibrosis of the intestine surrounding UC-associated tumors, which was not found in our series, the diagnostic criteria for evaluating the invasion depth of sporadic colorectal cancer by EUS might not be able to be used. Further studies of larger numbers of cases are needed, and studies strictly comparing EUS findings with histopathological findings of surgically resected specimens should be performed. These points have been added to the last part of the Discussion section.

(2) Reviewer 2 suggestions : In the original article of Kobayashi et al. the authors aimed to evaluate the clinical usefulness of EUS in the diagnosis of the invasion depth of colitis-associated tumors. They found that EUS provides a good estimation of the tumorous invasion depth. Though the case number is small, this manuscript seems to be the only one focusing on this topic. Using large search engines I could not find similar articles. Their results are of clinical importance as CAC is usually aggressive and hard to treat in advanced case. However, the authors mentioned that inflammation may result in an overestimated invasion depth of tumor. How can one discriminate between the inflammatory tissue and cancerous one with EUS? The figures are all help the understanding, the used references are up-to-date. Only some typo/grammatical mistakes can be found in the text, they must be corrected. After minor revision I suggest to accept the manuscript for publication in WJG.

Response

We previously performed a basic study of surgically resected specimens of UC and reported that the wall structure of the inflamed intestine on EUS became unclear in the presence of deep ulcers and inflammation, and that the findings on EUS were usually consistent with the histopathological findings (ref. 16). The UC-associated tumors in our study showed narrowing of, and breaks in, the colonic wall structure on EUS in association with deep invasion, which may be difficult to distinguish from histologic changes due to inflammation. However, UC-associated tumors were depicted as a localized mass on EUS, and this feature can facilitate differential diagnosis from histologic changes associated with diffuse intestinal inflammation. However, the presence of severe intestinal inflammation and fibrosis around UC-associated tumors (although not found in our study) can lead to the overestimation of invasion depth by EUS. Further studies of larger numbers of cases as well as analyses strictly comparing EUS findings with the histopathological findings of surgically resected specimens should be performed. This point was added to the last part of the Discussion section. In addition, the finding that UC-associated tumors were depicted as a well demarcated, isoechoic or hypoechoic localized mass by EUS was added to the Results section. This paper was reviewed by a native speaker of a translation company in Japan. However, we

additionally received language evaluation by the American Journal Express recommended by your journal.

(3) Reviewer 3 suggestions : This paper addresses an important and widely-investigated area dealing with the well known risk of long standing ulcerative colitis (UC)-associated tumors. However, the authors didn't show a clinical/gastroenterological approach to the problem rather a mere endoscopic approach. I means that evaluating the risk-benefits of an endoscopic treatment of such complication of long standing UC (i.e., dysplasia or cancer) a correct clinical approach requires an accurate description of the extension of the disease and of the clinical course of the disease itself, previous pharmacological treatment the patients underwent (i.e, 5-ASA, steroids, immunomodulators or biologics) and, above all, the possible requirement of anti-TNF therapy in the next future for patients with a high value for the Mayo score. The latest, is the most important issue required because of the well-known risk of cancer induced by Anti-TNF compounds.
Indeed, the use of most of biologics is contraindicated in patients with a previous history of cancer or high grade dysplasia. It means that patients underwent to an endoscopic resection of colon cancer will not allowed to receive this type of drugs in case of a severe clinical relapse of the disease. However, even if some authors would suggest that adenoma-like DALM can be resected endoscopically irrespective of the grade of atypia, provided that there is no evidence of cancer or dysplasia in other parts of the large intestine, I think that this approach is suitable in only a very small percentage of selected patients and cannot represent a standard treatment. On the contrary, EUS is most often used to evaluate colorectal cancer and helps to evaluate the depth of invasion of colorectal cancer on the basis of changes in the layer structure of the large intestinal wall on EUS thus allowing a correct endoscopic approach on removing the neoplastic lesion. In my opinion, this paper doesn't reach the standard of papers usually accepted for publication in WJG.I thank you for considering me as reviewer for this manuscript. Best regards,

Response
As you pointed out, most biologics are likely to be contraindicated in patients with a history of treatment for UC-associated tumors. In patients with UC at high risk for recurrence, total colectomy may be the procedure of choice on the diagnosis of UC-associated tumors. However, total colectomy may decrease patients' QOL because of factors such as frequent soft stools or fecal incontinence and increase the risk of pouchitis. UC-associated dysplasia may be difficult to distinguish from sporadic adenomas, which require different management, on conventional endoscopy. Differential diagnosis may be difficult even by EUS. As mentioned in the Discussion section, recent guidelines for the management of UC in Europe and North America have begun to recognize endoscopic resection as a treatment option for protruding-type adenoma-like dysplasia. For such lesions, EUS can be used to estimate invasion depth. As you suggested, endoscopic resection would be indicated for not that many lesions. In addition, even after endoscopic resection,

strict surveillance by colonoscopy is necessary in patients at high risk for tumors, and possibilities for drug therapy are limited in patients who have recurrence of UC. Fully informed consent about these issues should be obtained from patients.

(4) Reviewer 4 suggestions : The interest of this study is unclear because it does not change the management of the disease. However, it would be interesting to study if EUS highlights some anomalies around the neoplastic lesions and if it could be possible to distinguish the DALM form the ALMs.

Response

Conventionally, total colectomy was performed when UC-associated tumors were diagnosed, and the role of EUS was limited. However, recent treatment guidelines for UC proposed in Europe and North America recommend that the presence or absence of tumorous lesions in other parts of the colorectum should be rigorously evaluated on endoscopy before treatment and have begun to recommend endoscopic resection as a treatment option for protruding-type adenoma-like dysplasia. For such lesions, evaluation of the invasion depth by EUS may facilitate the selection of treatment and help to decide whether endoscopic resection is indicated. This point was added to the Discussion section. The degree to which various histologic changes of the intestine around UC-associated tumors can be recognized by EUS should be analyzed in studies comparing EUS findings with histopathological findings of surgically resected specimens. In our study, UC-associated tumors were depicted as clearly demarcated, isoechoic or hypoechoic mass by EUS, similar to sporadically developing colorectal tumors. These two types of lesions may be difficult to distinguish by EUS. However, this point should be analyzed in further studies of larger numbers of patients.

3 References and typesetting were corrected

Thank you for reviewing our manuscript in the *World Journal of Gastroenterology*

Sincerely yours,

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