05 March 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format.

Title: Lifetime risk of esophageal adenocarcinoma in patients with Barrett's esophagus (columnar-lined esophagus)

Author: Piers Gatenby, Christine Caygill, Christine Wall, Santanu Bhatacharjee, James Ramus, Anthony Watson, Marc Winslet

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
This study by Gatenby et.al, confirms and provides additional evidence supporting the low dysplasia/cancer progression rates in individuals with Barrett's esophagus. The study is well conducted and the authors also compare recent population-based estimates and apply to their own cohort. Following are my comments. 1) One of the major clinical challenges in this field is identifying those Barrett's patients who are at an increased risk of developing esophageal adenocarcinoma, which may depend on both genetic and environmental factors. It would have been useful if the authors can provide us with information on some of the epidemiological risk factors in their study cohort. For example, since obesity/high BMI etc. are considered general risk factors for cancer, have the authors estimated the Obesity rates in their Barrett's cohort at the entry point? Also, what proportion of their BE patients had reflux disease?
(1) Obesity rates in the UK were not generally well available (<20% available in the natural history study examining a subset of UK centres). The available data have been added to the introduction as well as a sentence on the rate of symptoms of gastro-oesophageal reflux. Data on age at diagnosis and gender are already available in the results section.

The manuscript of Piers Gatenby et al. evaluates and discusses an important question, namely the lifetime risk of esophageal adenocarcinoma development in patients with Barrett's esophagus (columnar-lined esophagus). Although the actuality of the topic is evident, it may not be accepted as it is, only after the suggested corrections. Major comment: Columnar lined esophagus (CLE) may not be used as a synonym for Barrett's esophagus. CLE includes gastric metaplasia as well (-> Montreal definition of GERD). According to the most recent AGA guidelines real risk for cancer development was established only in patients with specialized intestinal metaplasia (SIM). Furthermore, a recent work of Rosztoczy et al. (Digestion. 2011; 84(4): 273-80.) showed, that patients with different types of esophageal metaplasia and dysplasia have significant differences in the degree of their acidic and

biliary reflux. This paper should be mentioned in the introduction, after reference 1, since it has much more concrete data regarding the pathophysiological background of BE (and other esophageal metaplasias). As a consequence please indicate in the section of methods, that all of the studied patients had SIM. If this is not the case please indicate the percentage of patients with SIM. If patients with esophageal metaplasias other then SIM were included all of the studied parameters should be calculated for both subgroups (patients with and without SIM). Minor comment: Authors should add their own values to the tables in a separate row. This would improve the understanding of the results significantly

(2) The reference Rosztoczy *et al.* has been added after reference 1. The proportion of patients in the UK who have intestinal metaplasia detected at index endoscopy has also been added to the methods section as recommended. The ongoing question of the relevance of intestinal metaplasia with regard to cancer risk is a subject of ongoing research within the unit and further manuscripts will address this in greater detail in the future, consequently, the authors would respectfully request that we do not address this further in this manuscript. The authors have added their own values to tables 1 and 2.

The authors estimate the lifetime risk of development of esophageal adenocarcinoma or the combined end-point of high-grade dysplasia or adenocarcinoma in patients diagnosed with Barrett's esophagus. I have some minor concerns: 1. Is there any difference of lifetime risk of adenocarcinoma or adenocarcinoma and high grade dysplasia in combination between intestinal metaplasia-type and non-intestinal metaplasia-type Barrett's esophagus? 2. The discussion is too long and may be shortened.

(3) The question of the relevance of intestinal metaplasia with respect to cancer risk remains controversial. We have addressed this in the intestinal metaplasia paragraph of the discussion and further in the examination of the study of the Northern Irish pathology database. The discussion has been examined and shortened.

3 References and typesetting were corrected

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

Sincerely yours,

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