

Editor

The editing changes have been accepted and the manuscript formatted to comply with the editing rules.

Reviewer 02520549

We thank the Reviewer for his comment.

Reviewer 01047625

We thank the Reviewer for his comment.

Reviewer 02445450

This manuscript proposes new concepts that colon diverticulitis could indicate colorectal cancer existence. It is very interesting and educational, but may need further discussion regarding: pathological relationship between diverticulitis and oncogenesis; efficacy of surveillance of CRC using colonoscopic examinations. So please provide any suggestions regarding relationship between CRC oncogenesis and inflammation of diverticula. Also, if the authors could provide data what stages and pathologies of CRC have been found most in case of patients with diverticulitis, that would be very informative. In addition, colonoscopic exams are recommended every 5-10 years in usual cases, and 1 year after curative resection of CRC. If no CRC are found in cases of bleeding diverticulitis, for which colonoscopy should have performed for hemostasis, why CRC could mostly be found in 6 months, as the authors mention in this manuscript. Thank you.

We thank the Reviewer for his comment. The Reviewer highlights some very interesting points on the subject.

1. Relationship between oncogenesis and inflammation of diverticula

Diverticulitis and colorectal cancer are associated with similar environmental risk factors. Hence, one may argue that the elevated prevalence of colorectal cancer in patients with diverticulitis is likely to be epidemiological rather than causal. To illustrate this, the prevalence of diverticulosis is 48% among patients older than 50 y.o. in Australia ^[1] and the annual incidence of colorectal cancer is 0.04% in the USA ^[2], whereas these numbers are, respectively, of less than 2% ^[3] and 0.02% ^[4] in China. Some authors support, not without controversy ^[5], that diverticulosis may constitute, by itself, a risk factor for the development of colorectal cancer. For instance, Granlund et al. ^[6] performed a case-control study, comparing 41'037 patients with colorectal cancer to 82'074 patients without colorectal cancer and assessed whether or not these patients had been hospitalized for diverticular disease. They found that the odd ratios of colorectal cancer ranged between 22.75 and 31.49 six months after hospitalization for diverticular disease. Importantly, they showed that the risk of colorectal cancer decreased and reached the risk of controls after 12 months after hospitalization. Consistent with these results, in a previous study from our team ^[7], eight out of the 11 identified colon carcinomas were diagnosed within 2 months after index computed tomography, which represents the average time required to obtain endoscopic or surgical diagnosis. Moreover, radiological findings, mostly related to complicated diverticulitis, were identified as predictors of cancer ^[8-11]. Therefore, we suppose that the increased risk of cancer observed in the acute period after diverticulitis may result from the difficulties in distinguishing diverticulitis from colorectal cancer on computed tomography, especially in patients with

complicated diverticulitis. This has been mentioned in our Editorial : “The risk of CRC might be increased due to difficulties in distinguishing CRC from diverticulitis based on computed tomography, resulting in an initial misdiagnosis, despite the contribution of information bias that cannot be excluded.”

2. Stages and pathologies of CRC found in patients with diverticulitis

This data is unfortunately not available from large-scale studies.

3. Cases of CRC found after colonoscopy for bleeding diverticulitis

In our center, we do not perform early colonoscopy in patients with diverticulitis. However, in case of bleeding from diverticular disease (in the absence of inflammation/diverticulitis), we perform early rectosigmoidoscopy/colonoscopy for diagnostic and haemostatic purposes. In that situation, the probability of missing a colorectal cancer is very low.

In the study by Grahnat et al., the authors identified that hospitalization for diverticular disease in the previous 6 months constituted a risk factor for colorectal cancer. This was probably due to an information bias (colonoscopy) and/or misdiagnosis (bleeding/inflammation due to colorectal cancer misattributed to complicated diverticular disease). That increased risk disappeared after 6 months (time to obtain diagnostic endoscopy), suggesting that uncomplicated diverticular disease itself does not constitute a risk factor for colorectal cancer (cf. question 1). That point is discussed in the manuscript.

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