Author's response to reviews

Title:Frequent co-occurrence of high-grade dysplasia in large flat colonic polyps (>20 mm) and synchronous polyps.

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Author's response to reviews: see over
Dear Prof. Dr. Vogel,
Dear Dr. Kallenberg and Dr. Vleugels,

we would like to thank you for your careful reading of our manuscript and your many helpful comments and suggestions. We made several changes in our manuscript and added supplementary data. The changes in the text are depicted in red.

Review 1 (Dr. Jasper Vleugels):

(1) We changed the title of our manuscript to have a stronger focus on our key message

(2) We agree that we did not point out clear enough that we only focused on large flat polyps >20 mm in our study. Therefore, our findings are specific for this group of polyps and do not represent features of large polyps in general. We made several changes in the main text and title to clarify this point. To our knowledge, removal of large flat adenomas >20 mm are mainly conducted in tertiary centers because they are generally considered difficult to resect, and the majority of international publications describing histological features or locations of large flat sessile colonic polyps are from academic centers 1–3. The characteristics we found for our cohort was comparable to other published cohorts, as discussed in the first section of Discussion.

(3) As opposed to large flat adenomas, large penduculated polyps can be easily removed by snare and this is performed in primary or secondary medical centers as well. Including penduculated polyps would have introduced an unwanted bias towards the most complicated cases. To underline that we only focused on flat adenomas, we changed the title accordingly and made several changes in the main text.

(4) We fully agree that including macroscopic features such as Kudo pit pattern would provide more information regarding detection of polyps with adenocarcinoma. However, the available endoscopic reports did not provide such information in the majority of cases. We reviewed all endoscopy reports of flat polyps with adenocarcinoma regarding results from biopsies prior to...
removal and local staging. This additional information can be found in Supplementary Table 1 and we also added our findings to the Results section (page 8, lines 16-17, page 10, lines 16-17).

(5) Changes in the main text were made.

(6) Hyperplastic polyps larger than 20 mm and located in the rectosigmoid were included in the analysis of large polyps (see Table 1). Small hyperplastic polyps (>5mm) in the rectosigmoid were also counted if they occurred as synchronous polyps and summarized as serrated polyps as described in Methods (page 6, line 17-19).

(7) Features of synchronous polyps are described in Table 3. We made changes to the title of table 3 to point this out more clearly.

(8) We reduced the number of tables with regression models.

(9) Additional citations were added (e.g. page 12, line 1-2 and 3-4).

(10) We agree that data in figure 2 and the statistical model is not sufficiently explained and added amendments in the Results section (page 11, line 1-10). However, we still think that the information provided by this figure is of interest, because we used a statistical approach to define cut-off values that segregate populations with distinct histological characteristics. This information is useful for clinical routine.

(11) Presence of hereditary polyposis could not be comprehensively ruled from the available clinical data. However, several facts speak against polyposis as a major bias: 1. The median number of detected synchronous polyps was 3.8 which is much too low for FAP, the most frequent form of hereditary polyposis, or even attenuated FAP. 2. Development of polyps in patients with hereditary polyposis syndrome usually occurs at a young age and prophylactic colectomy is advised. In contrast, the mean age of our patient cohort was 65.4 years. 3. As part of an ongoing project, we distributed a detailed questionnaire on comorbidities among our patients with large flat polyps that also included a question regarding hereditary colorectal cancer predisposition (HNPCC/FAP). So far, of 361 completed questionnaires, only 7 patients had a hereditary predisposition.

Review 2 (Dr. Frank Kallenberg):

(1) As a tertiary center, we receive patients with difficult to resect polyps from either ambulant gastroenterological practices or other medical centers. Usually, large polyps in general or polyps located in the proximal colon are considered as difficult-to-resect cases. The group of large flat colonic polyps > 20 mm, which we focused on in our manuscript, represents a particular case that – to our knowledge - is mainly resected in tertiary centers because they are almost always considered as difficult-to-resect. A comparison with previous publications that investigated the same group of large flat/sessile colonic polyps shows that our observations are comparable and therefore unlikely to be significantly biased (see first section of Discussion). However, we agree that we did not point out clear enough that we only investigated large flat polyps. We made adaptations in our title and main text to clarify that we focused on this particular group of polyps.

(2) This was pointed out by Dr. Vleugels as well and we agree that detailed description of macroscopic features would have provided addition information. We reviewed all endoscopy
reports from polyps with adenocarcinoma. The majority of endoscopic reports did not have a standardized documentation of morphology, thus a meaningful analysis was not possible. However, biopsies prior to removal did not reveal presence of adenocarcinoma in most cases (see Suppl. Table 1, and page 10, line 16-17).

(3) We completely agree and added this point in our discussion (page 14, line 2-5).

(4) There is no difference and we have changed the text accordingly to avoid any confusion. We also adjusted the title.

(5) We have added a Supplementary Table (Supp. Fig. 2) showing the most important features for the three histological subtypes and added information in the Results section (page 8, line 12-13, page 9, line 5-7).

(6) Polyp size was determined by the endoscopist using the forceps or snare as a reference. This information was added to the Methods section (page 6, line 4-6).

(7) EMR was performed by senior endoscopists. This information was added to the Methods section (page 6, 5-6).

(8) We added this point to our discussion (page 13, line 27 to page 14, line 2).

(9) This question was also raised by Dr. Vleugels and is discussed extensively above (see point 11)

(10) We subdivided the discussion into smaller segments with headings.

(11) There is considerable evidence showing that EMR is a very safe method for removal of large polyps 4–7. Although we did not obtain data on adverse effect during EMR for our cohort, we think that it is worthwhile mentioning.

(12) The definition of serrated polyps is mentioned in the Methods (page 6, line 17-19). The categorization into specific histological subtypes is performed by the pathologist according to polyp morphology. In Table 1, we show the percentage of sessile serrated adenomas with low- or high grade dysplasia.

(13) This point was also raised by Dr. Vleugels. We still think that this Figure is worth showing, as it offers cut-off values that are more useful in clinical routine to identify high risk polyps. However, we agree that it is not well explained and therefore added a more detailed description (page 11, line 1-10).

(14) We changed the text accordingly.

(15) We changed this passage.
References:


We hope that all points could be covered to your satisfaction. Please contact us if you have any further questions or suggestions.

Yours sincerely,

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