Response to World Journal of Gastroenterology Critiques

Reviewer #02941416

1. Though the authors mentioned ADR as colonoscopy quality control in the Discussion section, this was not mentioned in the analysis. I suggest that the authors include this in the Results section to help the readers understand that all mentioned studies met the ADR recommendations.

Response: We have summarized the following information in the results text of our manuscript:

"Six of these studies met the accepted quality indicator threshold for overall adenoma detection rate (ADR) >25% among study patients,[9] including one study that explicitly described that ADR was >25% for each individual endoscopist in study.[10] ADR was only 22% in the study by Bonithon-Kopp et al[11] and the meta analysis by Saini et al. did not present information on ADR.[12]"

2. Did any of the studies mention an increased risk if multiple criteria for advanced adenoma were met. For example a subject with a high grade adenoma of 1cm may have a lower risk than those of high grade, villous adenoma of 1cm. I understand that retrospectively reviewing past studies makes this difficult. However, it would be of interest to the readers if multiple risk factors indeed increase the risk.

Response: No study explicitly compared the risk of future advanced adenomas at surveillance based on having multiple different risk factors simultaneously, likely due to issues around sample size and loss of power with these subgroup comparisons. However, if multiple independent risk factors were identified then having those simultaneously would increase a patient's overall risk of future

advanced adenomas. For example, in the study by Chung et al, number and size of adenomas at baseline were independent risk factors for future neoplasia. We have added the following to the discussion:

"Lastly, the existing data do not explicitly compare the risk of future advanced adenomas at surveillance based on having multiple different risk factors simultaneously, likely due to limitations of sample size and loss of power with subgroup comparisons. However, if multiple independent risk factors were identified (e.g. multiplicity and size), then having those simultaneously would increase the individual's overall risk of future advanced adenomas."

3. The studies included have a median follow-up period of 2-5 years excepting one study by Bertario (2003). I believe that this period is too short to draw firm conclusions. This may be mentioned as a limitation in the Discussion section.

Response: Thank you for this comment. We have added the duration of follow-up as a potential limitation in the Discussion section.

"The duration of follow-up for most of the studies ranged from 2 to 5.5 years, which does not allow for the assessment of long-term outcomes. However, this time frame is in line with current surveillance guideline recommendations and provides an adequate follow-up period for the evaluation of the risk of recurrent neoplasia."

Reviewer #00069471

1. Authors referred a lot of articles and analyzed the association of histologic features of adenoma and the risk of future colon neoplasia. However, there is no suggestion drawn from this analysis. For example, authors said that villous histology might have a small association with future advanced neoplasia. So do

they suggest that villous histology should not be a factor for advanced neoplasia? Authors did not mention that point.

Response: We have clarified the issue of villous histology in our discussion section as follows:

"Our review found that specific histologic features of adenomas (i.e. high grade dysplasia and villous features) are associated with a small risk of future advanced adenomas though data was inconsistent across studies (level B evidence). In particular, villous features did not confer a consistent or significant association, suggesting it may not be an important risk factor for future advanced adenomas."

Reviewer #03474228

1. My only concern is that authors did not mention the importance of the results of the National Polyp Study in discussion. To my knowledge, the current US guideline (especially regarding the recommended surveillance interval) was produced on the basis of the results of the National Polyp Study. I'd like to request the authors to interpret the results of the present study by comparing with those of the National Polyp Study in the discussion section.

Response: Thank you for this suggestion. We have summarized the National Polyp Study data and explained how it compares to our results. We have included this in the discussion:

"The findings of our study echo those of the seminal prospective randomized National Polyp Study, in which [32] multiple adenomas (≥ 3; OR 6.9; 95% CI, 2.6-18.3) and large adenomas (OR 2.2; 95% CI, 0.6-7.8) were associated with future advanced adenomas at surveillance. In that study, however only multiplicity was

a significant risk factor ($p<0.001$). The risk conferred by villous features or high grade dysplasia at baseline was not included."

Reviewer #03551966

1. There are many guidelines published with respect to surveillance protocols. Would the authors comment and perhaps summarise some of these guidelines in a table based on the colon adenoma features. Would the differences in guidelines perhaps be linked to national economics rather than disease prevalence? Would these protocols be different according to different continents as well?

Response: We had presented a summary of guidelines from three societies in Table 3 in the original manuscript. If the editors feel that a table of recommendations based on colon adenoma feature is more instructive, we can include a different version of Table 3, which is included in the manuscript now. We have also added the following to the Discussion text:

"While guidelines may be based primarily on adenoma features and risk of future neoplasia, they may also be influenced by national economics and local culture around population-based screening and surveillance, which can vary by country and continent."

Alternate Table 3.

Scenario	**Recommendations for surveillance, yrs**		
	USMSTF on CRC 2012	British Society of Gastroenterology* 2010	European Society of Gastrointestinal Endoscopy 2010
1-2 small adenomas	5-10	5-10	10
3-4 small adenomas	3	3	3

≥ 1 ≥ 10 mm	3	1	3
≥5 small adenomas	3	1	3
adenoma with villous histology	3	-	3
adenoma with high grade dysplasia	3		3
adenoma ≥ 10 mm	3	3	3
Serrated polyps			
< 10 mm no dysplasia	5	-	10
≥ 10 mm	3	1	3
dysplasia	3	-	3
traditional serrated adenoma	3	-	3

* The British Society of Gastroenterology guidelines account for number and size of adenomas but not histology.

2. Would the identification of colon adenoma features be different leading to different surveillance rates? The authors have alluded to biopsy measurements but would narrow band imaging and other methods be useful? Perhaps the authors can comment on those.

Response: The studies included in this review did not use specific technologies such as narrow band imaging or other adjunctive techniques. Some of these techniques have been shown to improve adenoma detection rates in certain circumstances (e.g. trainees and endoscopists who do not meet quality benchmarks). Accordingly, they may help detect more adenomas and put patients in higher risk categories than they may otherwise have been in the past. As a result, these patients may be recommended to return for sooner surveillance (e.g at 3 years instead of 5 years). While the use of these adjunctive techniques is outside the scope of the current review, we have mentioned their potential influence on surveillance intervals as suggested by the reviewer.

"As ADR improves overall whether from improved endoscope optics or adjunctive techniques (e.g. narrow band imaging, caps, rings),[37] the association between baseline colonic neoplasia findings and risk of future neoplasia may need to be reassessed."