20 March 2020

Answers for the Reviewer

Dear Reviewers,

Thank you for your comments. Here are the answers for these questions.

Reviewer 1.
Comment:
I have a few comments, only : Why do I need two Stages for low and high risk groups, each ? In my eyes one stage for low and high risk is enough ! Please explain in detail !

Answer:
There are only two groups in TAIM staging, low and high cancer risk. In OLGA and OLGIM stagings there are five risk groups (0-IV), and division to low risk (stages 0-II) and high risk (stages III-IV) is used in the literature, and we use this same division. Then readers can easier compare our results to the earlier ones.

Comment:
Why do you think TAIM is better with a specificity less than 50 %. Please explain in detail and set it into context with OLGA and OLGIM.

Answer:
The reviewer highlights this important issue: there are limitations when predicting the gastric cancer risk by using OLGA, OLGIM, and TAIM stagings. In our patient materials, the overall gastric cancer risk was low, and majority of gastric cancers were detected in low-risk groups in OLGA and OLGIM stagings. The specificity was better in these stagings when compared to TAIM staging. In TAIM staging majority of gastric cancers were detected in high-risk group. There were more patients in TAIM high risk group compared to high risk OLGA and OLGIM groups. TAIM and OLGIM stagings showed statistically significant differerence between different stages. Our results showed that these two stagings are preferrial compared to OLGA. The other reviewer raised the same question, see also the answer to the comment No 6 later.

Comment:
Furthermore , I would like to know the frequency of H.pylori Infection in all stages. Please base all calculations differently for individuals that are H.pylori positive , Those who had a prior infection and those who were always negative.

Answer:
Unfortunately, we have only the results from histological analyses, but no serological ones. Histological samples were taken from the patients in the screening gastroscopies. Finnish Cancer Registry does not have information of H. pylori-infections, and data is not achievable from the Population Register Centre either. Unfortunately, we don't have information of earlier H. pylori status, even this is an important issue. The overall frequency of H. pylori infections has been added to the Table 1. H. pylori positivity in all OLGA, OLGIM and TAIM

stages are represented in Table 4. In our study, H. pylori incidence might be underestimated. An article by Kokkola *et al*, showed that over half of the patients with positive H. pylori serology, had negative histology. (Kokkola, A *et al.* Scand J Gastroenterol 2000. 35(2), 138-41. Diagnosis of Helicobacter pylori infection in patients with atrophic gastritis: comparison of histology, 13C-urea breath test, and serology.)

Comment:
I also would like to know the percentage of autoimmune gastritis among the participants. I bet that TAIM, OLGA and OLGIM work for autoimmune gastritis and corpus dominant H.pylori gastritis best ! Please set this in context with the rather small patient numbers!

Answer:
In our material no autoantibodies against parietal cells or intrinsic factor were determined. There were 259 men who had marked atrophic gastritis in corpus, and no atrophy in antrum biopsies. Some of these men might have had an autoimmune gastritis. Eight of these men developed gastric cancer. Because autoantibodies were not determined, we cannot say how many of these men had autoimmune origin. This issue is now added to results section, and reflected on discussion.

Reviewer 2:

1.In this study, authors evaluated efficacy of TAIM system. At first, authors should evaluate whether score of each category is appropriate (for example: “Mild atrophy/IM in Antrum is 1” is appropriate).

Answer:
When designing the TAIM scoring system, the system was builded based on earlier European guidelines, and OLGA and OLGIM stagings. We considered three-tier staging (low-moderate-high risk), but concluded this two-tier scale more appropriate. This makes staging easier to use for the clinicians, but is not as detailed as the guidelines (does not consider the risk factors like family history, incomplete or complete form of IM etc.). Division of classification was considered appropriate, and therefore each category is not separately discussed.

If the reviewer suggests, that in TAIM staging the cancer risk should be assessed with same manner as in OLGA and OLGIM (Stages 0-IV), we do not think this is best option, because TAIM has only two categories, and in OLGA and OLGIM stagings stages I and II represent low-risk cancer groups. This might make misinterpretations when all three stagings are discussed.

2. Please make Table including patient’s characteristics.
Answer: New Table 1 has been created to introduce patient characteristics. In text, one sentence has been crossed out due to same information as is in Table 1.

3. Please add p value in Figures.

Answer:
P-values exist in the figures already.

4. In this study, one patient in OLGA I developed gastric cancer. This might not be H. pylori-related gastric cancer. Therefore, background of this patient may differ from others.

Answer:

This is correct. The H. pylori data is not sufficiently comprehensive. We have only histological samples, no serology. One explanation is that this patient had a H. pylori induced superficial gastritis without atrophy. Sampling error can be another explanation.

5. At least, the category of no atrophy/IM in antrum, corpus and whole stomach will be better to be none, not low. How do you think about it?

Answer:
The reviewer is correct. The risk of gastric cancer is very small, if patient does not have atrophy or IM in the biopsy specimen, and does not have foreknown risk factors. In our materials, the risk was not non-existing. One patient (1/74) who did not have atrophy or IM in the whole stomach, developed gastric cancer. We have to underline that our material is biased and does not represent general population, because men in our study were heavy smokers with low PGI, and mean age was over 60 in the beginning of the study. In general, if the patient has normal biopsy specimen, he/she does not go further for follow-up. The lifetime risk is minimal, but not totally non-existing. We wanted to avoid too many categories in this study, and did not want to exclude 74 patients without atrophy / IM.

6. It is unclear whether new staging system, TAIM, which divides patients into low- and high-risk groups of developing gastric cancer, depending on the degree of the atrophy or IM, is better than OLGA or OLGIM. Authors will be required to investigate efficacy of TAIM by validation.

Answer:
Based on our results, we cannot declare TAIM staging to be better than previous stagings. OLGA staging has lower interobserver agreement among pathologists, and OLGIM is considered to be better in the literature. Our results support these findings. Existence of IM indicates more advanced process in the stomach, which also emphasizes the use of OLGIM. For clinicians, it is troublesome to use two different stagings instead of one. Our results showed that gastric cancer risk increased statistically significally with the stage in OLGIM and TAIM stagings. It is notably, that TAIM low risk was the only group that did not have statistical significance with the cancer risk compared to general male population. OLGA and OLGIM both low (0-II) and high (III-IV) cancer risk groups and TAIM high risk group showed statistically significant difference compared to general population. TAIM showed the negative predictive value: patients in low risk TAIM group did not have statistically significant increase in gastric cancer risk compared to general population.

7. Many patients of East-Asian infected with H. pylori had severe atrophy and moderate-to severe intestinal metaplasia: TAIM High III-IV. Therefore, It will be better to divide patients with TAIM staging system high grade into two or three category group.

Answer:
This is a good point, and might show differences between high- and low-risk countries. In Finland, the gastric cancer incidence is only 5/100 000 for men, and 600 gastric cancers are diagnosed in the whole country per year. The distribution of patients into several groups would also divide gastric cancers into more groups leading to poor specificity with TAIM. This division to three or even more categories would not work out in our materials, but the situation can be different in high-risk countries.

Other notes:
Patient characteristics are presented in Table 1. Few P-values and n's were changed to italic (P->*P,* n -> *n*). Table 7 (now Table 8) was rearranged technically, no changes in values. Added text is in red color. Few sentences are crossed out, because same things are presented in Table 1.

Kind regards,
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