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September 30, 2015

To the Editors:

Thank you for the thorough and comprehensive review of our manuscript, "Anal cancer and intraepithelial neoplasia screening: a review." We wrote this article to help guide clinicians during a period of flux and uncertainty for the early diagnosis of anal cancer. The biomolecular understanding of anal neoplasia has benefited from the ongoing efforts to better understand cancer biology of other squamous cell cancers, but the clinical evidence for early detection still remains sparse. Our review of screening practices attempts to capture current consensus while also recognizing the paucity of evidence for aggressive screening of anal neoplasia.

We also sincerely appreciate the effort of the journal's reviewers. We have provided a complete response to all of their concerns on the following page.

All authors have approved this revised version of the manuscript and the analysis and discussion herein has not been previously published. Thank you for consideration of our revised manuscript. Please feel free to contact me at any time should you need further information.

Sincerely,

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REVIEWER #1
I think that this paper is well-written and very interesting for surgeons and gastroenterologists. In addition, this review is worth publishing in World Journal of Gastrointestinal Surgery.

We appreciate the kind words and recognition by Reviewer #1.

REVIEWER #2
This is an interesting paper and may be published, but some prerequsites should be added. Like in other screening projects, as for example abdominal aortic aneurysm screening, some questions have to be answered before screening recommendations can be given, especially if such programmes have to be payed by the insurance companies. a) Which are the groups that should be screened now exactly ?, defined by annual incidence rates (which must be known) and the prevalence. To this no details and data were presented.
The World Health Organization for many decades has employed Wilson's Criteria for what determines an effective screening test (in brief):

1) An important public health problem.
2) Known treatment.
3) Facilities available for diagnosis and treatment.
4) Presence of latent stage of disease.
5) Known diagnostic test.
6) Test is tolerable to patients.
7) Natural history of disease is well known.
8) Policy agreement on population at-risk.
9) Total cost per early detection is reasonable compared to late presentation.
10) Case-finding must be sustainable in continuity.

Thank you for your input on helping us to develop the structure of our paper for anal cancer screening.

We have added what is known of annual incidence rates of anal intraepithial neoplasia, prevalence, and natural history of disease, as suggested above (see new highlighted sections). In addition, we have added a description of the ongoing ANCHOR study (see new highlighted sections), which is currently studying whether anal cancer screening and treatment/ablation will ultimately decrease the incidence of anal cancer.

In this study, we elected to focus on Wilson's criterion #1, #3, #4, #5, #6, #7, #8, and #9 with secondary emphasis on criterion #2, #9, and #10. As we discussed in the introduction on pages 5 and 6, the hard clinical evidence for anal cancer screening is lacking. Given the lack of good epidemiologic or controlled trials data, we used this manuscript to explore what is known, what is unknown, and what can be practically done with the available literature.

What we believe Reviewer #2 expresses concern about is combination of Criterion #6, #8, and #9 with a particular focus on the Bayesian concepts of screening. In order for a screening test to be cost-effective, it needs to have a high sensitive and high specificity. Any limitations of the test's diagnostic accuracy will be amplified in a population with low disease prevalence with a higher rate of false-positives, false-negatives, or both. The data about diagnostic test quality is already summarized in Table 1. Most of this information is based on small studies that do not routinely place tests in head-to-head comparison with firm research methodologies.

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This policy argument for what populations to screen is particularly difficult without better epidemiologic data. Incidence of anal cancer in the general population is noted in the introduction (Page 4). Small studies have identified anal cancer risk factors to include HIV status, HPV status, smoking, and organ transplantation (Page 5). The lack of good data in this respect is a recurring theme of the paper. Trends in incidence that may affect future screening needs as well as future studies that will shape our understanding of disease burden in select risk populations is highlighted in the later portions of the manuscript (Pages 13-16).

b) Screening makes only sense if the prognosis of the screened population can be improved by this measure. This is not proven at all! So, for example, breast cancer screening in women is very popular but its benefit is very small. In fact, only a randomized study comparing patients at risk with and without screening for longer observation periods can give an answer. As long as such studies are lacking the benefit of anal cancer screening is theoretical and cannot be claimed. At best, the conclusion of this paper may be that patients at risk should be screened in an observation study (registry) and followed over longer periods to gain more facts to this problem.

Reviewer #2 highlights an important concern that anal cancer screening benefits are theoretical and cannot be strictly advocated for based on the evidence. We appreciate this viewpoint and agree that the scientific evidence in its current state cannot independent support routine screening for anal cancer precursor lesions. In our review, we went to great lengths to note that much of anal cancer screening practices are a logical extension of cervical cancer screening practices. In addition to noting the lack of good scientific evidence for anal cancer screening in our introduction (Page 5 and 6), for specific testing modalities (Page 10), in our unanswered questions section under Areas of Uncertainty (Pages 13-15), we also note that future recommendations may be guided by upcoming data from the SPANC study (Page 15).

Finally, like Reviewer #2, we emphasize the need for full-fledged randomized trials and longitudinal registries to identify whether anal cancer screening has a meaningful impact on the overall cancer burden faced by the population. This is addressed in our discussion entitled, "Future Directions." Of note, we have also included details of the ANCHOR study, which is a prospective randomized control trial that evaluates whether screening and ablation of HSIL will ultimately decrease the incidence of anal cancer.

CHANGES REQUESTED BY EDITOR

1. Conflict of interest statement signed and uploaded with submission. The statement has also been included in the edited version of the manuscript resubmitted.
2. Per Dr. Wen Lingling, the Core tip may be used as the 100-word summary outline highlighting the most innotivate and important arguments. Per Dr. Qi Yuan, the Core tip has been recorded as an audio file and uploaded with the submission.
3. Reference formatting has been updated as requested.
4. Figure 1 is a figure provided by non-author colleagues. Once the manuscript is accepted and in pre-press, we will seek formal permission for publication and provide you with an editable version.
5. The following first pages have been uploaded as documents without PMIDs:
    - American Cancer Society, Cancer Facts & Figures 2015
    - SEER Stat Fact Sheets: Cervix Uteri Cancer
    - National Cancer Institute, Pap and HIV Testing

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- New York State Department of Health, AIDS Institute
- National LGBT Cancer Network: Anal cancer, HIV, and gay/bisexual men
- NCCN Clinical Practice Guidelines in Oncology: anal carcinoma
- The Anchor Study website
- NCI Anchor Study announcement

6. The manuscript has been updated based on formatting guidelines in Guidelines and Requirements for Manuscript Revision-Review.
7. Grammarly plagiarism analysis and Google Scholar search results are uploaded with the submission.