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Title: Sampling error in the histological work-up of rectal neoplasms

Author Name: GMJ Bokkerink

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Dear Editor,

Thank you very much for the valuable comments of reviewer 02512504. The transparency of the "Express Submission and Peer-review System" is a good example of how modern research should work! In anticipation of the comments of subsequent reviewers, we adjusted the manuscript. You will find the changes in the new manuscript and an extra explanation in red below the suggestions of reviewer 02512504 in this document.

Thank you for the interest in our research.

Yours sincerely,

Guus Bökkerink

Reviewed by 02512504

Bkkerink et al describe the use of macrobiopsies in the diagnosis of rectal cancer. The question is of relevance and the data of interest. The authors should, however, clarify a few points:

It should be clarified that this is a retrospective study - Despite this is a retrospective analysis, it should clearly be stated whether there was a clinical protocol or the procedure was just depending on the physician in charge.

The presented flow chart was the standard procedure, as prescribed by the physician in charge of the diagnostic procedures for rectal neoplasms (co-author AB). Furthermore we adjusted the title. See below.

Why were 27 patients not further analyzed by rigid endoscopy?

We added the following explanation in the results section → “Rigid rectoscopy and macrobiopsies”:

The remaining 27 patients did not undergo additional macrobiopsies because there was no clinical suspicion of malignancy and endorectal ultrasound did not show invasion deeper than the submucosa (clinical benign or clinical T1). Further management was not dependent on histology analysis, since these lesions were regarded as indication for TEM for complete removal.

Please clarify. The title is misleading: Based on a retrospective analysis an overall sampling error, i.e. a sensitivity of the conventional biopsy cannot be assessed.

We adjusted the title. The value of macrobiopsies and transanal endoscopic microsurgery in the histological work-up of rectal neoplasms; a retrospective study.

We wanted to refer to “biopsy-sampling error” (as stated in for instance [this article](http://www.nature.com/bjc/journal/v111/n6/abs/bjc2014396a.html) <http://www.nature.com/bjc/journal/v111/n6/abs/bjc2014396a.html>) rather than to the statistical “sampling error”.

The title should be more modest (e.g. Impact of macrobiopsies in the histological workup of rectal neoplasms)

We adjusted the title(see above)

Ethical statement: The ethical statement is insufficient: Basically, this is an interventional study which should have an ethical statement by an Ethical Committee (please give a reference number of the local EC). In addition, a reference (literature or homepage) should be given for the statement that “the study was exempted from informed consent according to Dutch regulations”.

This was a retrospective evaluation of a clinical algorithm implying no other than established techniques, which was used during the study period. The data were collected from medical reports. It was not an interventional study. We added a reference to the Dutch Central Committee on Research Involving Human Subjects to <http://www.ccmo.nl/en/non-wmo-research>.