

December 22, 2015

Dear Editor,

please find enclosed the revised version of our manuscript entitled: "CT Colonography for the practicing radiologist: a review of current recommendations on methodology and clinical indications".

In the revision all of the reviewers' comments have been addressed giving a point-by-point reply to each query. The paper has also undergone extensive English language review.

I decided to change the authors order in respect to the efforts spent in the preparation of the manuscript, so that Paola Scalise is the first author and I, as team coordinator, take the last position.

I hope the manuscript has improved and look forward to your comments.

Best regards.

also on behalf of the co-authors,

Prof. Emanuele Neri

Report to Reviewer 1 (Reviewer Code: 2896724)

Query 1A

This study consists of narrative review study that aims to illustrate the current literature concerning CT colonography to better delineate its major clinical indications and the most updated recommendations on the technique methodology. This subject seems relevant because describes updated indications to CT colonography proposed by the recent ESGE/ESGAR consensus. Also the method for answering the research question seems appropriate, although it could be more systematic and rigorous. Congratulations for your work and for your contributions to improve our health. However, the structure and content of the manuscript needs minor improvements: -

The structure of manuscript is not classic one (introduction, material and methods, results, discussions and conclusion). It could result confused to reader.

Reply 1A

Dear Reviewer, concerning the structure of the manuscript, we adopted the format suggested by the Baishideng Publishing Group guidelines about the writing requirements for Reviews.

Query 2A

In the second paragraph of Introduction section two documents are cited: "... several European countries with significant reduction in number of deaths from CRC^{3,4}". It would more adequate supporting this affirmation with guidelines since the content of the phrase refers to recommendations about CRC screening.

Reply 2A

Thank you for your suggestion; we have modified the reference above accordingly to the comment.

Query 3A

In the fourth paragraph of Introduction section this text is included: "... in fact, even if the benefits of its employment in CRC mass screening have not fully established yet, (...)". However, there is a Health technology assessment report about efficacy, safety and efficiency of CTC colonoscopy vs optical colonoscopy for CRC screening. This report is available on:

http://www-csalud.dmsas.sda.sas.junta-andalucia.es/contenidos/nuevaaetsa/up/AETSA_2011_1_ColonoscopiaTAC_eng.pdf

Reply 3A

We modified the text and the corresponding references accordingly to the comment and the report provided.

Query 4A

For ESGE/ESGAR consensus the recommendations are followed of strong of recommendation and the level of evidence. In this manuscript the updating could include the same structure and highlight the changes that this update have added to original consensus.

Reply 4A

In our paper (which is not providing guidelines, because it is conceived in the format of a Review) we have not reported the level of evidence for each single literature reference. However, the reader can refer the guidelines provided by ESGAR, ESGE/ESGAR and ACR, cited in this review, to retrieve the level of evidence.

Query 5A

Also, the bibliography is wide and seems that the search developed have been comprehensive. So, the databases, search strategies and inclusion criteria could be described. Congratulations again for your work and for your contributions to improve our health.

Reply 5A

We included a thorough description of the search strategy used, the most important databases employed and the criteria applied to develop our research.

Report to Reviewer 2 (Reviewer Code: 00069608)

This paper reviews technique and clinical recommendations of CT colonography. Most of the pertinent literature is cited in the paper. The recommendations for CT colonography proposed by authors are in line with relevant studies in the field and with consensus statements by American Gastroenterological Association (AGA), American College of Radiology (ACR), and European Society of gastrointestinal radiology/endoscopy (ESGAR/ESGE). Major comments: none.

Minor comments:

Query 1B

“...most cancers develop from a small subset of adenomatous polyps due to sequential accumulation of mutations in specific genes[2].” Reference n. 2 does not seem appropriate for this statement. Please verify.

Reply 1B

We modified the text and the corresponding references accordingly to the comment and the report provided.

Query 2B

“...it is indicated in FOBT-positive or symptomatic patients and as preventive strategy in patients at increased risk of CRC[5].” Reference n. 5 is not entirely appropriate for this sentence. Please verify.

Reply 2B

As requested by Reviewer 2, we added a further reference to support appropriately the sentence in the text.

Query 3B

The sentence "...recent randomised studies have shown no significant differences in diagnostic performance between CT colonography and OC have been showed for clinically relevant polyps in a population of asymptomatic average-risk individuals[10]." is not clear and needs language polishing. Do authors refer to the randomized trial published by Stoop EM et al. Lancet Oncol 2012? Please revise.

Reply 3B

We agree with the referee and we reformulated the sentence as suggested, correcting the syntax mistakes.

About references, we specifically referred to the prospective study published by Pickhardt P et al in 2003 (Computed Tomographic Virtual Colonoscopy to Screen for Colorectal Neoplasia in Asymptomatic Adults); the randomized trial published by Stoop EM et al. Lancet Oncol 2012 was erroneously reported referring to the specific sentence, however it was already included into our bibliography and inserted in the section "Future emerging indications" above. Furthermore, as requested by the Reviewer 1, we added the "Health technology assessment report about efficacy, safety and efficiency of CTC colonoscopy vs optical colonoscopy for CRC screening" published by the Agencia de Evaluación de Tecnologías Sanitarias de Andalucía in 2013. We accordingly modified the relative references.

Query 4B

"CT colonography is also useful to demonstrate post-surgical colonic anatomy and offers information about wall morphology of the anastomosis[16,25,26]." References n. 25 and 26 do not seem appropriate for this statement. Please verify.

Reply 4B

As suggested, the inappropriate references have been removed and substituted with more pertinent ones to better support the statement.

Query 5B

"However, the role of CT colonography is controversial in estimating the parietal involvement caused by inflammatory bowel diseases (IBDs) and there are only few studies reporting the performances of CT colonography in such setting[39,40]" Reference n. 39 is not appropriate here. Please verify.

Reply 5B

Reference n. 39 has been removed in the final version of the review since it was erroneously cited referring to the specific sentence.

Query 6B

"...including magnesium citrate and (saline cathartics);...." This sentence seems incomplete. Please revise.

Reply 6B

Thank you for the notice. We correct the sentence (unfortunately part of the sentence had been accidentally deleted in the prior version of the review).

Query 7B

"Nevertheless, rare anaphylactoid reactions have been reported after its oral administration..." Authors should also consider this reference: Miller SH. Anaphylactoid reaction after oral administration of diatrizoate meglumine and diatrizoate sodium solution. AJR Am J Roentgenol. 1997;168(4):959-61 -

Reply 7B

Thank you about the hint. We added the suggested paper in our list of references.

Query 8B

Reference n.71 is cited before ref. n. 70 (page 12).

Reply 8B

Thank you for the correction; we fixed the erroneous numbering and order of the cited references.

Query 9B

“Colonic lesions detection is highly influenced by maximum collimation; for this reason, narrow collimations not exceeding 3mm, are recommended [23, 84]. In particular, according to the ESGAR consensus, a collimation of less than 3 mm is currently endorsed[56].” The repetition in these sentences should be avoided.

Reply 9B

We agree with the Referee; the entire sentence has been reformulated trying to make it clearer to the reader.

Query 10B

“....no statistically significant difference in terms of sensitivity and specificity among 2D and 3D reading strategies has been reported in literature[105].” This statement is apparently in contradiction with the study by Pickhardt cited a few lines above, which showed a reduced sensitivity of 2D approach. Please consider revising these sentences.

Reply 10B

According to the comment of the Referee, we revised the text in order to avoid contradictions and to underline that the best approach (2D/3D) to use for primary search of colorectal polyp and cancer is still controversial and under debate.

Query 11B

“However, even if second read CAD may increase sensitivity for polyp detection,...” Authors should cite a proper reference here, such as: Regge D, Della Monica P, Galatola G, Laudi C, Zambon A, Correale L, Asnaghi R,Barbaro B, Borghi C, Campanella D, Cassinis MC, Ferrari R, Ferraris A, Hassan C, Golfieri R, Iafrate F, Iussich G, Laghi A, Massara R, Neri E, Sali L, Venturini S, Gandini G. Efficacy of computer-aided detection as a second reader for 6-9-mm lesions at CT colonography: multicenter prospective trial. Radiology. 2013 Jan;266(1):168-76

Reply 11B

The relevant trial proposed by the Referee has been inserted in the list of references and cited in the text.

Query 12B

“.....the advanced adenoma, defined as a lesion measuring ≥ 10 mm with high-grade cellular dysplasia[7,101].” For a definition of advanced adenoma authors should also consider: Winawer SJ, Zauber AG. The advanced adenoma as the primary target of screening. Gastrointest Endosc Clin N Am. 2002 Jan;12(1):1-9, v. Review

Reply 12B

We modified the definition of advanced adenoma in the text according to the definition provided by Winawer SJ et al; furthermore the paper proposed above has been inserted in the bibliography.