29690-ANSWERING REVIEWERS

Answer to peer reviewer NO one

As explicitly mentioned below, in your invitation letter it was stated that
"There is no restriction on number of words, figures, tables or references. Your paper will be published free of charge after peer review".
That is why we would like to ask you to specify if there is a real necessity to shorten the volume of our manuscript by reducing the number of the figures and tables. This is an open-access journal and such a limitation does not seem advisable and cost-effective. Our primary objective was to make an attempt to popularize the scientometric methodology among your extraordinarily broad international readership, if possible.
In this very concise peer review there is, however, an unpleasant grammatical error indicated in red for your convenience.

The authors explored five information portals for the topic of colorectal tumor markers and outlined the significant journals, scientists and institutions. The authors made a tremendous efforts on searching and comparing the five information portals, and showed the detailed results. This article seems to fulfill the purpose raised by the authors with comprehensive collection of relevant publication in a systematic way. Although the authors' efforts should be appreciated, 7 figures and 15 tables would be too many for one article. The authors should select only relevant figures/tables and make the article fit the journal style described in instruction for the authors. All the other less important figures/tables could be submitted as supplementary files.

Answer to peer reviewer NO two

The true merit of a scientometric treatise consists in providing specific and systematized information for science policy makers and scientists themselves about the actual trends in science development in a given field of discipline, usually, at the forefront of research. The factual information that could be immediately used by readers is presented in several tables and is limited predominantly to journal titles, author's names, nominations of leading institutions, as well as bibliographic data about most-cited papers. The claim in the peer review that 'only numbers of papers and journals are cited" is therefore, incorrect.
Single scholars who are active in the interdisciplinary field of colorectal tumour marker(s) can select from the ocean of scientific literature the most suitable publications by themselves. Young readers, however, could become easily familiar with the hot topic when considering the most productive actors worldwide.
The publication containing these terms in their titles only were retrieved and subsequently analyzed. The paper suggested for eventual citation does not seem appropriate as the term of 'colorectal tumour marker(s)' does not exist neither in its title, nor in its abstract (see the abstract attached below for your convenience). Besides, in this peer review containing a total of three sentences and 49 words, there are three (!?!) orthographic errors indicated in red for your convenience.

The authors performed an enormous work on the international literature. However, the interested reader finds no systematic citation of the diferent methods and they did not weigh them agains the others. The work is completely useless for prectical gastroenterologists , as only numbers of papers and journals are cited. Specific comment.: The authors forgot to cite an important article: Gastrointest Endosc. 2015 82:133-7. doi: 10.1016/j.gie.2014.12.048. Epub 2015 May 16. Survival in patients with

colorectal cancer diagnosed by screening colonoscopy. Friedrich K(1), Grüter L(1), Gotthardt D(1), Eisenbach C(1), Stremmel W(1), Scholl SG(2), Rex DK(3), Sieg A(4).

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Survival in patients with colorectal cancer diagnosed by screening colonoscopy.
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BACKGROUND: In Germany, screening colonoscopy was first established in 2002 aspart of the national cancer screening program.
OBJECTIVE: To evaluate whether colorectal cancer (CRC) survival differs when CRC is diagnosed by screening colonoscopy (S-CRC) versus diagnostic colonoscopy (D-CRC).
DESIGN: Long-term, retrospective, multicenter, observational study.
SETTING: Study centers: 10 private gastroenterology practices in Germany.
PATIENTS: A total of 60 patients diagnosed with CRC during screening colonoscopy and 252 patients during diagnostic colonoscopy in 2002, 2003, and 2004.
INTERVENTIONS: Colonoscopy.
MAIN OUTCOME MEASUREMENTS: Survival of patients up to December 2013.
RESULTS: Mean (±standard deviation [SD]) follow-up time was 81.0 (±40.1) months. Union Internationale Contre le Cancer (UICC) stages I and II were found more often in S-CRC (81.6%) compared with D-CRC (59.9%; P < .002). Kaplan-Meier analysis showed significantly reduced overall survival for patients with D-CRC (mean [±SD] 86.9 [±3.0] months; 95% confidence interval [CI], 81.0-92.8) compared with S-CRC (mean [±SD] 107.1 [±4.9] months; 95% CI, 97.4-116.9; P = .003). When deaths not related to CRC were excluded, survival was still shorter for D-CRC patients (mean [±SD] 89.4 [±3.0] months; 95% CI, 83.5-95.4) compared with S-CRC (mean [±SD] 109.6 [±4.7] months; 95% CI, 100.2-119.0; P = .004).
LIMITATIONS: Retrospective study design.
CONCLUSION: In this long-term, retrospective study, patients with CRC diagnosed during screening colonoscopy lived significantly longer when compared with patients with CRC diagnosed during diagnostic colonoscopy.

Answer to peer reviewer NO three

The objective of our manuscript was to try to make the young readership familiar with the capacity of modern computerized scientometrics to facilitate the orientation of the scientists and clinicians involved in coloproctology research in the ocean of scientific literature on a given hot-topic.
We have inserted additional explanatory texts immediately dealing with most recently published applications of colorectal tumour markers for a variety of purposes such as diagnosis, including early diagnosis, prognosis, survival and evaluation of therapeutic effectiveness as follows:

i) in the INTRODUCTION section:
Better understanding and elucidation of the various influences provides a more accurate picture of the segmental distribution of some common molecular markers in colorectal cancer such as KRAS, EGFR, Ki-67, Bcl-2, and COX-2, potentially allowing the application of a novel patient's stratification for treatment based on particular molecular profiles in combination with tumour location[11].

ii) in the DISCUSSION section:

Modern colorectal tumour markers are used either for diagnostic, or for prognostic purposes. In addition, they could be applied for therapeutic evaluations.

The combined detection of two tumour markers, serum p53 antibody and carcinoembryonic antigen (CEA), improves the diagnostic sensitivity and prognosis of early-stage colorectal cancer patients[14].

A diagnosis strategy of serum tumour markers, an artificial intelligent algorithm, provides decision support for physicians on the usage of different tumour markers and diagnosis of colorectal cancer[15].

CEA containing macrophages combined with C-reactive protein possesses diagnostic potential in early colorectal cancer[16]. The diagnostic models based on the logistic regression analysis, support vector machine and back-propagation neural network demonstrate a higher early diagnostic value of the combination of serum tumour markers, e.g. CEA, cancer antigen (CA) such as CA 19-9, CA 242, CA 125, and CA 15-3 for colorectal cancer[17]. SATB2 protein is a diagnostic marker for tumours of colorectal origin and provides a new and advantageous supplement for clinical differential diagnostics[18]. In combination with CK7 and CK20, its specificity increases from 77% up to 100%. The most common markers for such tumours include the expression of CK20, often along with lack of CK7, i.e. the CK20+/CK7- phenotype[18].

MYBL2 gene is an independent prognostic marker with tumour-promoting functions in colorectal cancer and its overexpression may play an important role in tumourigenesis [19]. HLA class II antigen expression in colorectal cancer is a reliable prognostic marker as it is related with a favourable clinical course of the disease[20]. The combined high levels of some inflammatory cytokines such as CXCL8, vascular endothelial growth factor and Pentraxin3 are potential prognostic markers as they are associated with increased risk of colorectal cancer recurrence independently of TNM staging and with worse survival[21]. The circulating microRNAs markers miR-122 and miR-200 family members could be used in the development of a multi-marker blood test for colorectal cancer prognosis and survival[22]. The decreased erythropoietin expression, high vascular endothelial growth factor levels and elevated cyclin B1 expression, predominant moderate tumour differentiation, absence of metastasis, and negative lymph node status are reliable proliferation and differentiation markers indicating the low level of aggressiveness, better prognosis, and longer colorectal adenocarcinoma patient's survival[23]. By means of solid-phase proximity ligation assay, 35 protein markers were simultaneously analyzed in a small amount of blood of stage I to IV colorectal cancer patients, however, these markers did not give better prognostic information than CEA[24].

An outlined correlation exists between the differentiation degree and expression of aldehyde dehydrogenase 1, a stem cell marker, in colorectal carcinoma cells[25]. Low-stage tumours exhibit a higher expression of aldehyde dehydrogenase 1 or CD133 compared with high-stage tumours while CD133 expression is associated with lymph node metastasis-positive cases thus predicting the disease prognosis. Aldehyde dehydragenase 1 and Nodal are important prognostic markers in colorectal cancer as there is a significant correlation between their expression and the differentiation degree, metastasis, number of tumour-positive lymph nodes and disease stage[26].

In the CONCLUSION section:

Contemporary colorectal tumour markers are more and more widely studied and routinely applied in clinical coloproctology worldwide thus promoting the further improvement of individualized patient's management.

In fact, although the publications devoted to the diagnostic usage of the colorectal tumour markers predominate within this relatively rich collection retrieved in four information portals, there are several papers containing more than one concrete purpose of these markers (see, for instance, the paper co-authored by M. Kunizaki et al., Clinical value of serum p53 antibody in the diagnosis and prognosis of colorectal cancer. *Anticancer* Res 2016; **36**: 4171-4175).

The added text and references are indicated in red and bold in the revised version of the manuscript for reviewer's convenience.