Professor Andrzej S Tarnawski

Editor-in-Chief

World Journal of Gastroenterology

Re: Revision of an invited manuscript

Dear Professor Tarnawski,

Thank you for considering our revised manuscript “Survival in early-onset oesophageal adenocarcinoma: a systematic review and meta-analyses” by AC Russell, S Mitchell, R Turkington and HG Coleman. We welcome the comments and helpful suggestions made by the reviewers. We have responded to each of the comments below and have carried out revisions to the manuscript as suggested by the reviewers on both submissions. We agree that these changes have strengthened the manuscript and we hope that it is now suitable for publication in the World Journal of Gastroenterology.

The paper is an original research article, undertaking a systematic review and meta-analyses investigating survival in early-onset oesophageal adenocarcinoma (OAC), defined as a diagnosis of OAC in adults aged less than 50 years.

Globally, the incidence of OAC is increasing. In addition, an increase in incidence of early-onset OAC, has been observed. Despite early-onset OAC being diagnosed at more advanced stages than OAC in older adults, evidence regarding survival is conflicting and limited. A systematic review in this area is urgently needed and to our knowledge this is the first study to investigate this area. Our results suggest that OAC does not carry significant differences in survival between age groups, but up to date, high quality, population-based studies are required in the future.

To set the study in context, the epidemiological landscape of cancer incidence is changing, and the incidence of early-onset cancers, largely accepted to be in adults aged under 50 years, is increasing. This includes an observed increase in the incidence of gastrointestinal malignancies such as colorectal, oesophageal, gastric and hepatobiliary cancers. There is an urgent need for research in this field, including treatment regimens and outcomes. At an international level, the transatlantic Cancer Grand Challenges program has announced nine new challenges in their most recent funding call, one of which is early-onset cancers, highlighting the urgency and global nature of the changing epidemiology of cancer incidence. We therefore feel this paper reflects a relevant, insightful and timely research project.

No ethical approval was required or sought for this project, as no new primary data was generated.

Author Professor Helen Coleman has several years of experience in epidemiology and statistics, and in addition consulted with a colleague who is a Professor of Medical Statistics with regards to the meta-analyses techniques used. Therefore, we consider the manuscript to have undergone biostatistics review.

In regard to competing interests, Dr Ashleigh Russell (née Hamilton) is an independent speaker for Bristol-Myers Squibb, and has received payment for lectures, presentations, speakers bureaus, manuscript writing or educational events (independent Speaker – paid directly by BMS).

Neither this paper nor any part of its content has been submitted or accepted for publication elsewhere. This manuscript has been contributed to, read and approved by all authors and they accept responsibility for the manuscript content.

Correspondence regarding this paper should be directed to Dr Ashleigh Russell or Professor Helen Coleman at the following address:

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We look forward to your review and welcome any additional queries about this manuscript.

Respectfully,

Dr Ashleigh Russell and Professor Helen Coleman (on behalf of the authors)

Reviewer 1

Authors response to reviewer: Thank you for your insightful comments and feedback. By incorporating these suggestions the manuscript has been strengthened.

Consider starting the introduction with a brief statement about the significance of studying early-onset oesophageal adenocarcinoma (OAC) specifically, before discussing the broader epidemiological trends.

Response: We have adjusted the beginning of the introduction as suggested, with the first sentence now relating to early-onset OAC.

While in methods it's mentioned that a protocol was composed using PRISMA guidelines, providing more detailed information about the protocol (such as registration number if registered, specific inclusion/exclusion criteria) is necessary.

Response: We have added additional information at the start of the methods section, detailing what was included in the study protocol. The inclusion and exclusion criteria are also outlined in the Methods section.

The search strategy can be more detailed. Mentioning specific keywords or MeSH terms used, as well as any Boolean operators or filters applied, is important.

Response: We have added information on the search strategy, relating to the groups of keywords and MeSH terms searched for ie. The categories of young age, survival outcomes and oesophageal cancer. Due to word count constraints we have outlined the keywords and MeSH terms used in the Supplementary file 1.

The process of data extraction and quality assessment can be presented better. For example, provide more details on the criteria used in the Newcastle-Ottawa Scale and how discrepancies between reviewers were resolved.

Response: We have expanded on the detail on data extraction and quality assessment in the methods section.

When discussing the studies excluded after full-text review, provide more detail on the reasons for exclusion. A brief summary of the main reasons (wrong study population, irrelevant outcomes) could be helpful.

Response: We have expanded on this in the text, and the reasons for exclusion are also shown in Figure 1.

In discussion, explain more the potential biological differences, variations in treatment approaches, or disparities in healthcare access that might explain why some studies report better outcomes for younger patients while others do not.

Response: The discussion around our findings is very interesting, with many factors contributing. We have expanded the discussion as suggested, covering the biology of OAC, treatment disparities, and inequalities in accessing healthcare.