Author’s response to reviews

Title: Patient-Reported Outcomes in Randomised Clinical Trials of Bladder Cancer: An updated Systematic Review

Authors:

Mieke Van Hemelrijck (mieke.vanhemelrijck@kcl.ac.uk)

Francesco Sparano (f.sparano@gimema.it)

Debra Josephs (debra.josephs@kcl.ac.uk)

Mirjam Sprangers (m.a.sprangers@amc.uva.nl)

Francesco Cottone (f.cottone@gimema.it)

Fabio Efficace (f.efficace@gimema.it)

Version: 1 Date: 31 Jul 2019

Author’s response to reviews:

This is an update of a prior article looking at the quality of patient reported outcome data in randomized trials on bladder cancer. The authors try to make a push for increasing inclusion of PROs in bladder cancer studies especially because of the advent of studies using immunotherapy drugs. I don't understand why that particular drug type matters. In my experience general QOL is way better in patients undergoing systemic therapy with IOs compared to multi agent chemotherapy, especially in metastatic disease. PROs become most important when these agents are brought in earlier, for example in NMIBC or in the adjuvant setting, and most of those studies are still underway (and as mentioned in the discussion, many are planning to include PROs). They are also appropriate when the treatments are designed specifically to improve symptoms or side effects (such as the robotic vs open cystectomy or adoption of ERAS preoperative techniques).

In fact none of the studies they identified were using systemic therapy - they included 4 studies that were basically anesthesia studies or studies evaluating treatment of pain during or after procedures. While this is fine, it doesn't really match with the focus of the introduction or discussion.

I would suggest the authors remove the discussion about immunotherapy in the introduction and decrease the focus in the discussion as well. I also think there is another reason that PROs are not reported with the detail required by the ISOQOL is the tight word limits of most journals. If the PRO is a secondary endpoint and is not significantly different between the two arms, there
is not usually space to describe the kind of detail required by these guidelines. Compliance would basically require a completely separate article focused on just that aspect - good luck getting that published if the results are negative! In addition, the tools we have to study QOL in specific cancer/treatment situations are quite limited.

RE: Thank you for your comment. Based on the experience of our clinical colleagues immunotherapy (especially checkpoint inhibitors) may have a different effect on QoL. However, we appreciate the reviewer’s point that to date very few studies have been published. As per the reviewer’s suggestion, we have therefore removed the paragraph from the introduction section. We have kept it in the discussion as this will be important for future studies.

With respect to your second suggestion, we have now added the following sentences to the discussion: “Furthermore, it is worth highlighting that the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group has developed various tumour and treatment-specific QoL Modules – with several currently in development, including specific ones for non-muscle invasive BC, muscle invasive BC, and metastatic bladder cancer (41). Finally, it is important to note, however, that word limits in journal guidelines may sometimes limit authors in the opportunity to report on secondary outcomes (i.e. PROs) for their trials – especially if the results for the primary outcome are negative. ”

A couple of other specific comments:

1) In the results section (p 8) the authors report "of the seven newly identified studies...", but in the rest of the manuscript and tables they report 8. Where did the other one go?

RE: Apologies for this typo. We have now corrected this throughout the manuscript into “eight”.

2) In the discussion p 11 they noted only 295 studies in the 3 years 2015-18, which is about 100 per year - the same average in 2004-2014. This is not really relevant. They should just say they only had 3 years of data to discuss and in fact the % of RCTs including PROs did increase during this current period, from <1% to about 3%.

RE: We thank the reviewer for this remark. To address this comment, we have deleted the sentence from the discussion section.