PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Quality of life of elderly patients with solid tumours undergoing adjuvant cancer therapy: a systematic review
AUTHORS	Cheng, Karis, Kin-Fong; Lim, Ethel, Yee-Ting; Kanesvaran, Ravindran

VERSION 1 – REVIEW

REVIEWER	Heike Schmidt Institute of Health and Nursing Science, Martin Luther University Halle-Wittenberg, Germany
REVIEW RETURNED	03-Jul-2017

GENERAL COMMENTS	Comments to the authors, This systematic review addresses the very relevant topic of health related quality of life in elderly cancer patients undergoing adjuvant therapy. Especially as older cancer patients have not been represented and included adequately in studies in former times, the research question, whether global QoL declines or improves during and following adjuvant therapy is of great importance. Minor comments: General: 1. As the review is referring to health related quality of life (HRQoL), I would suggest the expression 'global HRQoL' instead of "global or overall QoL". 2. Some language editing would be advisable to further improve the readability of the paper. 3. The source of funding should be reported. Major comments: Abstract: Methods: 4. The given research aim "to examine the literature" is too global and does not correspond with the review question on page 5 which is more specific. 5. The years considered in the search should be reported ("from inception"?). 6. Referring to the PRISMA checklist, data sources, inclusion criteria (study design), and appraisal and synthesis methods should be specified. Results: 7. The design of the included studies (e.g. observational, RCT) is of interest for the interpretation of the results. 8. The decline of QoL of patients with glioblastoma should be specified (e.g. clinically or statistically significant). Text:

	Method: For comments referring to the PRISMA checklist, the number of the respective item is given. 9. Please comment on the non-availability of the protocol and registration number (5). 10. Please specify the years considered and the date last searched (7). 11. The complete search strategy including limitations etc. should be presented as recommended in the PRISMA checklist, to allow a rerun (8). The fact, that a recent paper on quality of life in very elderly radiotherapy patients by Kaufmann et al. 2015, which would meet the inclusion criteria, was not found in the search leads to doubts concerning the choice of keywords and the search strategy. 12. The references given for assessment of the methodological quality of the included studies are other systematic reviews. I would recommend to utilize guidelines e.g. by the Cochrane library, the Agency of Healthcare Research and Quality or the Joanna Briggs Institute (12). 13. Page 7: data synthesis: Please clarify also with respect to the study design, which studies qualified for meta-analysis. Results: Search results and study characteristics 14. In addition to the given summary score for methodological quality (table 1) a risk of bias table showing the specific items and authors' ratings should be provided to allow for a reconstruction of the process (19). 15. As the review includes observational studies and interventional studies, a separate reporting of the risk of bias could be considered. 16. Page 8 line 30: "items where neither met the criteria …". Does this sentence refer to included studies or to excluded studies? 17. Page 9 and table 1: The authors describe 13 studies as observational studies. Ref. no. 21, Gallego et al. (2011) is a prospective phase II study and ref. no. 24, Minitti et al. (2013) is a secondary data analysis of a phase II study. Please harmonize text and table 1. 18. In table 1, ref. no. 16, Dees et al. (2000) included n=11 patients ≥65 years plus n=6 patients ≥70. The results presented cover only patients ≥65 who completed QoL baseline assessment (n=11). Accordingly the no. of subjects who completed baseline QoL should be corrected in table 1. 19. Page 9: Sample size … This paragraph could benefit from restructuring to enable referral to the preceding paragraph where observational studies and RCTs are described separately. 20. Page 9: As far as I can see, the study by Caffo et al. would not meet the defined inclusion criteria ("Studies that covered heterogeneous age groups were included where subgroup analyses was provided …"), as sample size was not reported for patients ≥65 and therefore no subgroup analysis was presented. In addition, baseline scores of QoL are not reported in this study and QOL scores are solely derived from the one item question of the diary card. Instruments (page 9 line 34 and following): 21. Brief descriptions of the instruments with references and the respective scores included in the analyses would be of interest to the reader.

	22. In my opinion, the attribution of the Perceived Adjustment to Chronic Illness Scale (PACIS), as QoL measurement is questionable. In the cited reference (Hürny 1997) PACIS was used as one of 4 single items (physical well-being, mood, appetite and PACIS (perceived adjustment/coping)). Hence I am skeptical about the comparability with the other studies included in the review especially since quality of life research and the development of instruments have advanced since the publication date of this study (2000). 23. The M. D. Anderson Symptom inventory was designed as patient-reported outcome measurement tool for symptoms and their interference with functioning. In the abstract of the paper by Mohile et al., 2011 the tool is described accordingly: “Patients rated 10 symptoms and their interference with daily function and QOL on a Likert scale from 0 (not present) to 10 (as bad as possible).” As to my understanding, QoL was not assessed separately, it is questionable whether this study meets the inclusion criteria. 24. Page 10, line 23: The comparison of QoL at differing measurement times and for various study cohorts is certainly a challenge. Comparison is further complicated as only 7/18 included studies reported co-morbidities (p. 10 line 23). This should be addressed in the discussion. Results: 25. Page 12, last paragraph: Perrone et al. reported in the conclusions of their abstract that docetaxel “worsens QoL and toxicity”. In the text they report no statistically significant differences between both groups for global QoL and functioning scales. However the graphs in the supplement show considerable differences between baseline and cycle 3 (global HRQOL -10; -18) and a large clinically significant difference for role functioning for the docetaxel group. These facts might be of interest in connection with the chosen topic and referred to in the discussion. 26. Page 15 line 47 and following (see also comment no. 22): This paragraph would benefit from some clarification. As I understand the description, in this study, one item measuring the interference of symptoms on QoL was included in addition to the core set of items of the MDASI. As I understand the results, interference of symptoms on QoL was low at baseline and reported slightly increased at the completion of RT. Discussion: 27. In the first sentence QoL should be replaced by HRQoL because “a patient’s overall appraisal of the impact associated with the cancer and its treatment” to my mind is the definition of health related, disease specific quality of life. 28. Page 17 line 23 and following: ”Our review suggests that elderly patients can tolerate adjuvant therapy without compromising their QoL in the long term” and line 43 and following: “In general, adjuvant chemotherapy and radiotherapy have no longitudinal detrimental impact on global (…) in the elderly population”. These sentences are in my opinion not justified by the results of this review. In addition to the sentence in the conclusion mentioning correctly the heterogeneity of QoL measurement and lack of data, limitations possibly affecting the interpretation of the results should be discussed in detail e.g. limited available evidence, diversity of the included studies, with respect to the number of participants, design including measurement points (Giesinger et al. 2014), date of publication. In addition, the studies provide little or no information about supportive measures during treatment and after care that are surely influencing QoL in the long term.

	29. While aspects of individual assessments of QoL and response shift are discussed well (page 18), in addition the limited sensitivity of change of global HRQoL and the resulting challenge to choose appropriate outcomes could be discussed in connection with the literature e.g. Wildiers et al. (2013), Giesinger et al. (2016), and (Derks et al. 2016).

REVIEWER	Kyriaki Mystakidou Pain Relief & Palliative Care Unit, Department of Radiology, Areteion Hospital, National & Kapodistrian University of Athens, School of Medicine. Greece
REVIEW RETURNED	03-Jul-2017

GENERAL COMMENTS	An interesting topic, thoroughly researched.

REVIEWER	Alyson Huntley University of Bristol, Uk
REVIEW RETURNED	20-Jul-2017

GENERAL COMMENTS	I think that this subject is really important. The systematic review has been conducted to good standards overall but i would like to question the lack of justification and rationale behind both the quality assessment and the meta-analysis. A lesser point to put the results in context with the greater literature especially any relevant qualitative studies Specifically: Quality appraisal I am not aware of a quality appraisal tool based around QoL but I accept that this could be a good idea but considering a relatively unknown tool there is no description of it and no justification for why it was chosen over the more conventional tools e.g. CAP RoB The 2005 reference given is as far as I can see just a previous use of the tool. Also very little space is given over in the results to the outcome - a number in the table is limited and one sentence on what was not quite up to scratch inadequate. If it a validated tool, the detail should be given. Perhaps it would be better if both CASP/RoB and this QoL measure should have been used alongside to compare and aid discussion on this tool. MA The review includes meta-analysis combining observational and RCT data - I am not sure that is methodologically sound (from my own experience) but I think it is on the whole fairly unusual. At the very least there needs to be some justification and supporting reference quoted. However the heterogeneity of the analysis says it all - it is massive and really puts into doubt this approach. Saying there is high heterogeneity (all round) is not a justification. Finally the authors conclude that these data support that older people deserve treatment too and that QoL arguments should not get in the way. The supporting literature appears to be all study/quantitative data - a supporting qualitative literature both from the patient and health professional would be in order.

	Overall I would only be happy with this paper being published if the meta-analysis was either removed or there is sound justification for its use. I have no problem with the data being presenting in forest plots but without the summation. Ditto the quality of life critical appraisal tool or as I suggested a comparison with more main stream accepted tools would add to the value of this paper. Thirdly a more patient centric discussion would greatly enhance the discussion and paper.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1's Comments

… I would suggest the expression 'global HRQoL' instead of "global or overall QoL".
Response/change:
It has to be depended on the scale being used by individual studies. For EORTC QLO-C30, it should be global QoL. For BCQ, FACT-B, etc, it is overall.

Comment: The given research aim "to examine the literature" is too global

Response/change:

We have edited the aim (p. 5)
Comment: The years considered in the search should be reported

Response/change:
We have specified this information in the search section (p.5).

Abstract

Response/change:
We have edited the abstract (pp. 203).

Comment: a recent paper on quality of life in very elderly radiotherapy patients by Kaufmann et al. 2015, which would meet the inclusion criteria...

Response/change:
Kaufmann, Schmidt, Ostheimer et al. Quality of life in very elderly radiotherapy patients: a prospective pilot study using the EORTC QLQ-ELD 14 module. 2015.
We excluded this article during our screening stage as it was NO separate QoL score reported for the group without metastatic cancer (68% subjects had advanced/ metastatic cancer in this study), and thus ineligible to be included in this review.

Comment: …I would recommend to utilize guidelines e.g. by the Cochrane library…
Response/change:

We have taken the suggestion of including RoB assessment seriously.
We have used the Cochrane RoB tool and Risk of Bias tool in Non-Randomised Studies of Interventions (ROBINS-I) for RCTs and non-RCTs to evaluate RoB of the included studies, respectively (pp. 7-8, 31-32).

Comment: … a risk of bias table showing the specific items and authors' ratings should be provided..

Response/change:
We have included a RoB figure and table (p. 33 Table 4; Figure 2).

Comment: As the review includes observational studies and interventional studies, a separate reporting of the risk of bias could be considered

Response/change:
We have included a separate figure and table on this (pp. 29-30 Table 3, 33 Table 4).

Comment: Please harmonize text and table 1.

Response/change:
We have edited these parts (pp.10-18).

Comment: The results presented cover only patients ≥65 who completed QoL baseline assessment (n=11). Accordingly the no. of subjects who completed baseline QoL should be corrected in table 1.

Response/change:
We have corrected this (pp. 11-17)

Comment: the study by Caffo et al. would not meet the defined inclusion criteria (”Studies that covered heterogeneous age groups were included where subgroup analyses was provided …”), as sample size was not reported for patients ≥65 and therefore no subgroup analysis was presented. In addition, baseline scores of QoL are not reported in this study and QOL scores are solely derived from the one item question of the diary card.

Response/change:
This study met the eligibility criteria for inclusion in the review as:
• It provided the baseline QoL and follow-up data (please see Table 2) for patients ≥65 years of age. (sample size and QoL data are different parameters) (p. 27)
We did not limit the QoL scale to be multi-dimensional (in particular in the geriatric setting).

Comment: …the attribution of the Perceived Adjustment to Chronic Illness Scale (PACIS), as QoL measurement is questionable…

Response/change:
The construct to subjective evaluations of QoL is still a matter of debate. We’d prefer to keep this study as the authors conceptualized QoL as a global indicator of the adjustment process which seemed makes sense to this context.

Comment: The M. D. Anderson Symptom inventory …: “Patients rated 10 symptoms and their interference with daily function and QOL on a Likert scale from 0 (not present) to 10 (as bad as possible).” As to my understanding, QoL was not assessed separately, it is questionable whether this study meets the inclusion criteria.

Response/change:
It is quite well-documented that adverse effects/symptoms in cancer therapy setting contribute a significant amount of variance to QoL, and hence, such measurement of QoL seemed makes sense to this context.

Comment: The comparison of QoL at differing measurement times and for various study cohorts is certainly a challenge. Comparison is further complicated as only 7/18 included studies reported co-morbidities (p. 10 line 23).

Response/change:
We have strengthened the discussion, and we believe sufficient emphasis is made (pp. 42-43).

Comment: In the first sentence QoL should be replaced by HRQoL because “a patient’s overall appraisal of the impact associated with the cancer and its treatment”...

Response/change:
QoL refers to the health-related QoL of elderly patients in this review. We have added an explanation note of QoL in introduction section to improve the clarity (p. 5).

Comment: Page 17 line 23 and following: ”Our review suggests that elderly patients can tolerate adjuvant therapy …., adjuvant chemotherapy and radiotherapy have no longitudinal detrimental impact on global (…) in the elderly population”. These sentences are in my opinion not justified by the results of this review…

Response/change:
We have edited these paragraphs as:

Comment: … that QoL during and after adjuvant chemotherapy and/or radiotherapy is maintained or improves in most of patients with solid tumours…

Comment: Adjuvant chemotherapy and radiotherapy may not have detrimental effects on global or overall QoL and other QoL domains in most elderly cancer populations (pp. 41 & 44).

Comment: … the studies provide little or no information about supportive measures during treatment and after care that are surely influencing QoL in the long term.

Response/change:
We have added the information about supportive care in Table 2 (pp. 20-27).
Only 2 studies mentioned briefly about supportive care, and thus it may not be able to substantiate the discussion.

Reviewer 3’s Comments
Comment: …a quality appraisal tool based around QoL but I accept that this could be a good idea … there is no description of it and no justification for why it was chosen over the more conventional tools e.g. CAP RoB The 2005 reference given is as far as I can see just a previous use of the tool. Also very little space is given over in the results to the outcome - a number in the table is limited and one sentence on what was not quite up to scratch inadequate. If it a validated tool, the detail should be given. Perhaps it would be better if both CASP/RoB and this QoL measure should have been used alongside to compare and aid discussion on this tool.

Response/change:
The quality appraisal tool was originally developed to assess the internal and external validity of prognostic studies and was modified to assess the methodological aspects of QoL reporting in later studies.

We have expanded the description and justification of this tool (p. 7).

Comment: In addition, we have taken the suggestion of including RoB assessment seriously.

We have used the Cochrane Risk of Bias tool and Risk of Bias tool in Non-Randomised Studies of Interventions (ROBINS-I) for RCTs and non-RCTs to evaluate RoB of the included studies, respectively (pp. 7-8, 31-32).

Comment: The review includes meta-analysis combining observational and RCT data - I am not sure that is methodologically sound (from my own experience) but I think it is on the whole fairly unusual. At the very least there needs to be some justification and supporting reference quoted.

Response/change:
We have taken this feedback seriously. We have removed the MA. The review results were synthesised narratively instead (pp. 34-35, 39).

Comment: Finally the authors conclude that these data support that older people deserve treatment too and that QoL arguments should not get in the way…

Response/change:
We have removed this sentence. In addition, we have revised the discussion and conclusion sections, in particular to in line with RoB assessment and review limitations (pp. 41-42, 44).