Author's response to reviews

Title: Prevention and treatment of acute radiation-induced skin reactions: a systematic review and meta-analysis of randomized controlled trials

Authors:

Raymond J Chan (email.rchan@gmail.com)
Joan Webster (Joan_webster@health.qld.gov.au)
Bryan Chung (Bryanc.dal@gmail.com)
Louise Marquart (louise.marquart@qimr.edu.au)
Muhtashimuddin Ahmed (Muhtashimuddin_ahmed@health.qld.gov.au)
Stuart Garantziotis (stuart.garantziotis@griffith.edu.au)

Version: 3
Date: 27 November 2013

Author's response to reviews: see over
Prevention and treatment of acute radiation-induced skin reactions: a systematic review and meta-analysis of randomized controlled trials

Referee 1

1. The methods state that inclusion criteria required that studies were RCTs providing a comparison between intervention types or between an intervention and no intervention; and that participants were those receiving external beam radiation. It is not stated that studies would be excluded if they did not report on any of the outcomes of interest. However, many of the excluded studies described in Additional File 2 were RCTs evaluating an intervention for managing RISR, which were excluded because the studies did not report on the outcomes of interest in the review. This inclusion criterion needs to be made explicit.

Authors reply: Thank you, please see “Trials reporting the outcomes of interest listed below were included.” is now added under the section if inclusion criteria.

2. Table 2 shows the results of the comparisons made by included studies, including results of meta-analyses, and some of these results are also highlighted in the text. The discussion highlights that confidence intervals were wide for most of the comparisons included in the review, but does not discuss the magnitude of the effects found. I think it would be useful to add some discussion around this (for example, are the magnitudes of effect large enough to make it worth changing clinical practice?) This would also be an appropriate place to discuss requirements for further research. For example, although cost was listed as an outcome in Table 1, no mention is made of it in the results (presumably due to the lack of data). Would you therefore recommend that cost is included in future trials of RISR prevention or management strategies? What else would you recommend? This is touched on very briefly in the conclusion, but would be worthy of further discussion.

Authors reply: Thank you, this review includes 48 studies. We believe that it would be redundant to discuss wide confidence interval on analyses that are not significant. With regards to costs, we have now added: “The results of review highlight that none of the studies measured all outcomes of interest. Some non-clinical outcomes (such as cost or costs associated treatment delay and labour) can be important for clinical decision making. Future trials should include these important outcomes”.

3. In the discussion, some limitations of included reviews are mentioned, such as that some therapies were only tested on particular anatomical sites or with certain radiation techniques, and that evidence may be “regarded as indirect for other areas”. Despite this, specific details are not provided. To really make this paper useful in guiding clinical practice, I would like to see more details of which populations, sites and techniques were examined by the included trials (perhaps in a table). This would enable clinicians reading this paper to determine if there is evidence relevant to their patients.

Authors reply: Thank you, we have now included a new additional table including all characteristics of the included trials (Please see Additional File 4).

4. In the discussion, the authors define the maximum level of RISR as “the worst reaction associated with a given intervention or no intervention at all”. This is a useful definition, but it would be more useful if the definition was provided in the methods section.

Authors reply: Thank you. This is now included in the methods section.

5. In the conclusion, it is stated that “non-metallic deodorant use is not contraindicated”. Although this may be so, the limitation of this sentence to only non-metallic deodorants suggests that there may be evidence against metallic deodorants. In the results, it is unclear in the prevention section if the evidence relating to deodorant use refers to metallic or non-metallic deodorants; the results from the treatment section suggest that neither metallic nor non-metallic deodorants impacted RISR outcomes. Can you please clarify the type of deodorant tested in the prevention studies and amend this sentence for clarity?

Authors reply: Thank you. We have now clarified this in the results section: “While it was thought that deodorant (both metallic and non-metallic) might have an undesirable effect on the skin, there were no differences in a number of RISR outcomes between those who wore deodorant or not as
In the conclusion section: “Consequently, clinicians may advise patients to gently wash affected areas with soap and water during their treatment and that non-metallic deodorant use is not contraindicated. Further research is required to establish whether metallic deodorants should be used.”

6. The abstract lists six types of interventions considered in the review (oral systemic medications; skin care practices; steroidal topical ointment/cream; steroidal topical ointment/cream; dressings and other). For consistency, it would be preferable if these matched the terms used in the body of the review; in results under study selection, the interventions are listed as “systemic oral therapies, non-steroidal topical therapies, dressing interventions, washing practices, deodorants/antiperspirants, and light emitting diode photo-modulation”.

Authors reply: Thank you. Please see the changes across the manuscript. Now the order is: oral systemic therapies -> washing practices -> deodorant/antiperspirant use -> steroidal topical therapies -> non-steroidal topical therapies -> dressing interventions -> light emitting diode photo-modulation. In the abstract section, these terms are in the same order, but simplified.

7. In the background section, fourth paragraph, reference is made to methodological issues in previous reviews, including “lack of duplicate selection of studies”. This wording may be difficult to understand – I initially believed the authors were talking about problems with reviews including multiple papers reporting on the one study (in which case, a lack of this would not be a problem), but on re-reading, realised the authors were talking about duplicate assessment of study eligibility. This could be made clearer.

Authors reply: Thank you. This has now been amended.

8. In the methods section, outcomes (primary and secondary) subsection, the authors state that they have adjusted the time points of the secondary outcomes, due to the “difficulty of measuring the commencement of skin reactions of every single participants of the trial” [sic]. Apart from correcting the grammatical error, the authors could make this easier to follow by stating that they had specified time points of secondary outcomes in their review protocol; it thus makes it easier to follow that they changed these during the course of the review and to understand why they were changed.

Authors reply: Please see changes: “During the review, we adjusted the time points of the secondary outcomes established in our review protocol. This was due to the difficulty of measuring the commencement of skin reactions of every trial participants. These outcome measures at the pre-specified time points were too restrictive and possibly unrealistic.”

9. Also in the outcomes subsection, and Table 1, reference is made to level of symptom severity (physical or psychological). It is not clear if the authors mean to include any symptoms reported, whether or not related to RISR, or if the outcomes are intended to only assess symptoms which are presumed to follow on from RISR or its prevention or management (and how it would be determined if the symptom was related). Further detail regarding this outcome and its rationale would be valuable.

Authors reply: Please see changes. Now it reads: *All symptoms reported by eligible trials were included. In Table 1.

10. In the data extraction section of the methods, it is stated that a data extraction form was developed, piloted and amended. I suggest adding details of how many studies the form was piloted with. Also in this section, it is stated that JW and LM checked the accuracy of data entry by independent data entry. I suggest adding details of how much data was independently entered (eg 10% or data from a certain number of studies?) and how this data was compared with the data entered by RC.

Authors reply: Please see changes. Not it reads: A data extraction form (see Additional File 3) was developed, piloted (with three studies) and amended. Two individuals, with at least one being RC or JW, independently extracted data using the data extraction form for each study. Any errors or inconsistencies were resolved after consulting the original source and consensus. RC entered the data into RevMan 5, with JW and LM checking the accuracy of all data entry.

11. The first sentence in the data synthesis and analysis section states that we “analysed data separately” using RevMan 5 – it is not clear what you mean by analysing data “separately”.
12. In the results section, study selection subsection, it is stated that 1851 citations were identified from the electronic database searches. However, Figure 1 shows that 8599 records were identified (4857 after duplicates removed). Please clarify.

Authors reply: Thank you. Please see changes. Now it reads: “The different steps of the electronic search are illustrated in Figure 1. In total, we identified 4857 citations from the electronic database searches after removing the duplicates. After we screened all the titles and abstracts, 105 articles were potentially relevant and we retrieved them in full text.”

13. In the results section, risk of bias assessment subsection, it is stated that studies were judged as being of unclear or high risk of bias for other potential sources of bias for various reasons (“(e.g. declarations of potential conflicts of interest or funding support were frequently unreported, or the report did not clearly state to what extent any support might have posed a risk of bias”), but it is not clear how cases studies were rated as being of “unclear” risk versus “high” risk.

Authors reply: Thank you. We made decisions based on whether there were commercial support and positive effects. However, if there is no acknowledgement of funding support at all, we classify these studies as “unclear” risks. This method is used for any other risk of bias assessment. Where we cannot establish high risk due to lack of information, we classify them as unclear risks. Where there is sufficient information specifying low risk of bias, we classify as “low risk”. This is a conventional practice in conducting systematic reviews using Cochrane methodology.

14. In the results, data synthesis section, in both the prevention of RISR and treatment of RISR sections, the dose of some of the oral systemic therapies is unclear. For example, in the prevention section, the dose of oral Wobe-Mugos E is listed as three tablets, four times a day, but the length of time during which the therapy was given is not specified (for example, was the therapy delivered for x many days prior to radiation treatment or during treatment only?) If this is too much information for the body of the review, suggest adding these details to Table 2.

Authors reply: Thank you, please see changes made: Now it reads. The two trials (32,33) had slight variation of daily dosage and days of administration before commencement of radiation treatment. We have highlighted these differences in the additional table outlining the characteristics of the trial and detailed information about the interventions.

15. In the results, data synthesis section, mention is made many times of ‘small’ studies and ‘small-to-medium’ size studies. I suggest providing some clarifications up front of what this nomenclature means (eg ‘studies with 50 or fewer participants were classified as small’).

Authors reply: Thank you. We have now added this under the 1st paragraph under Data synthesis and analysis: “We considered studies with less than 100 participants small, studies with between 101 to 200 participants medium and studies with more than 201 participants large.”

16. In the results, data synthesis section, treatment of RISR subsection, non-steroidal topical treatment, second paragraph: When discussing the trial of RadiaCare Gel and Aquaphor ointment, it is unclear if these treatments were tested separately or in conjunction. Initially, it says that the trial reported no statistically significant benefits of “RadiaCare Gel and Aquaphor ointment” (suggesting that they were used together), and then it said that “participants were more satisfied with these two interventions”, suggesting that each was tested as a separate intervention. This lack of clarity is also evident in the following sentences with regard to aloe vera gel and dexpanthenol, and qingdiyou medication, wheatgrass extract cream, and sucralfate cream.

Authors reply: Thank you. Please see changes made: “One trial with multiple treatment arms (40) also reported no statistically significant benefits of RadiaCare Gel and Aquaphor ointment when individually compared to placebo for reducing RISR, although the participants were more satisfied with these two interventions, compared with placebo topical preparations. According to the findings from the analyses in this review, we were unable to find any benefits of aloe vera gel and dexpanthenol, when compared with placebo or no treatment. While a number of trials individually reported statistically significant benefits of using qingdiyou medication, wheatgrass extract cream, and sucralfate cream for reducing RISR, we were unable to conduct analysis due to inadequate data despite attempts of contacting the trial authors.

17. In the same section as per the point above, it is stated that “we were unable to conduct analysis...”
despite attempts of contacting the trial authors”. Suggest you clarify if the inability was due to inadequate data being provided by the publications, and that the trial authors did not respond to contact.

Authors reply: Thank you, please see changes made: “we were unable to conduct analysis due to inadequate data despite attempts of contacting the trial authors”.

18. Table 2 – although some abbreviations have been defined, there are several used in this table that have not been defined and should be to allow the table to stand alone (eg RTOG, QoLC30, EORTC, RISR, CTCAE, NCI CTC, SE, SD, CI, LED

Authors reply: Thank you. Please see addition here: “Note. CI= Confidence Interval, CTCAE= Common Terminology Criteria for Adverse Events, HR= Hazard Ratio, LED=Light Emitting Diode photo-modulation, MD = Mean Difference, OR = Odds Ratio, RISR: Radiation Induced Skin Reactions, RTOG: Radiation Therapy Oncology Group, SD=Standard Deviation, SE=Standard Error.”

19. Figure 3, sample size of included studies: this chart is somewhat difficult to interpret as the sample size categories are of different sizes. Suggest showing sample size using interval data (histogram) or using categories of equal size (eg 1-50, 51-100, 101-150, etc)

Authors reply: Thank you. We have made changes accordingly in Fig 3.

20. Figure 4, risk of bias summary: suggest adding an additional column to show the overall assessment of bias assigned to each study

Authors reply: Thank you. There is no overall assessment. Each of the risk of bias assessment item was distinct.

21. There are some grammatical and typographical errors, and the manuscript would benefit from a clear read to identify and address these. For example:
  - Results section, study selection subsection: the “majority (n=29) of studies included less than 100 patients” should read “…fewer than 100 patients”
  - Results section, study selection subsection: “all studies were undertaken with adult patients except for one that included patients between 3-21 years of age” should read “…patients between three and 21 years of age”
  - Results section, risk of bias assessment subsection, third paragraph: “Of the 47 studies, 16 studies described sufficient detail in how binding of participants…” should read “… 16 studies described in sufficient detail how…”
  - Results section, prevention of RISRs subsection, oral systemic therapies: one small unblinded trial of 74 participants reported that “oral pentoxifylline is ineffective…” should read “… was ineffective”

  - Results section, treatment of RISRs subsection, non-steroidal topic treatment: “When it is compared with placebo” should be “when it was compared with placebo”
  - Results section, treatment of RISRs subsection, dressings: Two small non-blinded RCTs, “with less than 40 participants in each trial, reported examined the effectiveness…” – remove reported or examined. Also in this sentence, the RCTs examined the effectiveness of the dressings “on” time to healing (not “in” time to healing)
  - Results section, treatment of RISRs subsection, dressings: “silver nylon dressing were more effective…” should be “was more effective”
  - Abbreviations: RTOG should be “Radiation Therapy Oncology Group” (capitalise)

Authors reply: Thanks. We have made ALL changes according the reviewers suggestions.

22. In the results, data synthesis section, prevention/steroidal topical treatment subsection, the last sentence says that the “older trials” had small sample sizes. Suggest referring instead to the “latter” trials as the year of the trials in not provided with the referencing system used.

Authors reply: Thank you. This is now amended.

23. In the results, data synthesis section, treatment of RISR subsection, oral systemic therapies: the last sentence states that the “effectiveness of oral pentoxifylline, oral antioxidant, or oral sucralfate suspensions… was not found”. Suggest clarify if this is to mean that these therapies were not found to be effective, or that there was not data available (or couldn’t be found) to determine the effectiveness of the therapy.
The effectiveness of oral pentoxifylline, oral antioxidant, or oral sucralfate suspensions for reducing symptoms related to radiation treatment cannot be determined with the available data.

Table 2 lists the included studies by author name and date. It would be useful if the citation to the paper(s) was also given by numbering, as in the text, to allow the reader to more easily refer back and forth from the text and table. Suggest using consistent headings for additional files (Additional file 1 is not labelled with this name; Additional file 3 is labelled “Additional File X”).

Referee 2:

After application of the PRISMA Checklist I have the following comments:

1. In the introduction ("Background") I miss an explicit statement of the questions being addressed (#4).

Authors reply: Thank you. Please see changes made. Now it reads “Therefore, the aim of this systematic review was to assess the effects of interventions for preventing and managing RISR in people with cancer.”

2. Please hand in at least one search strategy (#8)

Authors reply: Thank you. Please see addition made to Additional File 1.

3. The Measures of consistency (heterogeneity) for the meta-analyses are lacking under “Methods - Date Synthesis and analysis” (#14).

Authors reply: Thank you. Please see the addition under the section of data synthesis and analysis:

Heterogeneity was tested using the $I^2$ statistic (which was used to describe the percentage of the variability in effect estimates that was due to heterogeneity rather than sampling error). A value greater than 50% was considered to represent substantial heterogeneity (26), and we explored heterogeneity and possible reasons. We undertook random-effects analyses if $I^2$ was greater than 50%.

4. Publication bias (#15, 22) is not mentioned in the manuscript. It might be not possible to assess because of the heterogeneity of included studies, but this has to be reported as well.

Authors reply: Thank you. Please see the addition: “With regards to the assessment of publication bias, it is recommended that a funnel plot should only be constructed when there are at least 10 studies in a meta-analysis (26). Therefore, we did not construct a funnel plot to assess the possibility of publication bias because there were too few trials per meta-analysis (all <3).”

Referee 3:

1. Searches were completed 11/2012, ie. a year ago. Since then there have been a couple of more papers published that are relevant. I would suggest that authors update their search before publication (my preference) or at least identify these studies and incorporate them in the discussion.

Authors reply: Thanks, please see the following addition:

Since the search of this review was conducted (11/2012), at least three trials [75-77] relevant to the research question of interest have been published. An RCT of 411 patients by Sharp et al reported no significant difference between Calendula Weleda® and Essex cream ® in reducing RISR [76]. Another double-blind RCT of 318 patients conducted by Graham et al also reported negative findings in their RCT on the effects of a moisturizing durable barrier cream and glycerine cream [75]. With regards to dressings, a small unblinded RCT (n=88) reported a significant reduction in
time to heal when Mepilex Lite dressing was used in comparison with the usual care group [77]. The results of this review suggest that the evidence base is extremely wide, with many interventions tested. However, evidence for any particular product remains thin, with very few trials examining the effects of any single intervention. Therefore, we do not expect the direction of recommendation to change with the additional trials published over this period. However, it is important that any subsequent trials should be included in the future updates of the systematic review. Multiple high quality trials comparing promising interventions are urgently needed.”

2. Some (Chinese medicine I think) products are also included, i.e., Lian Bai liquid etc., we don't really know what these are, please briefly describe what are they and their key constituents.

Authors reply:
Please see addition: “Lian Bai liquid is consisted of Huang Lian (Rhizoma Coptidis) 15g and Huang Bai (Cortex Phellodendri) 15g soaked in 800 ml of water.”