7 February 2015

Dear Dr Michael Yang

Thank you to the reviewers for their time and valued feedback. Please find below our responses to reviewers comments on our manuscript. Also please find attached copy of the updated manuscript with track changes made to the originally submitted manuscript.

Reviewer 1:

1) *This review identifies 24 additional symptoms of recurrence. However, the manuscript does not provide any guidelines to use the symptom checklist.*

See lines 307-316

This tool could be utilized in many ways. For example, it could be used by specialist consultants, general practitioners and registered nurses as a prompt at appointments to encourage discussion of symptom experiences, used as an educational tool checklist to increase patient awareness of common recurrence symptoms (based on discretion of health professionals), and may also be used in less traditional approaches to follow-up, such as over the telephone to discuss symptoms and/or to provide patient education. This symptom checklist is currently being tested for sensitivity and is used to trial a novel and less-intensive approach of surveillance that could potentially be used as an alternative to traditional surveillance method to detect recurrences as early as possible in endometrial cancer survivors.

2) *The manuscript also does not include any supporting data for the checklists.*

The article makes reference to recently published guidelines recommending that patient education on symptoms be the cornerstone of follow up practices. The symptom checklist is a method that can be utilized in a variety of ways (see Q1 response above) for example, as a prompt to increase patient awareness on the types of common symptoms that may indicate recurrence.

3) *The conclusion is not clear.*

See lines 364-373

The management of endometrial cancer follow-up remains controversial [Podczaski, 1992 #8] [Greven, 1987 #208] [Sears, 1994 #209]. There is an urgent need for a more efficient, effective and streamlined approach for endometrial cancer surveillance. Given that the majority of endometrial cancer recurrences present through symptoms and recently published guidelines recommended patient education on symptoms be the cornerstone for patients’ follow-up for recurrence detection [National Comprehensive Cancer Network (NCCN), 2013 #139;Reddoch, 1995 #102], the use of a symptom checklist tool could prove to
be successful as one modern alternative to follow-up care for endometrial cancer survivors upon completion of successful testing within a prospective study.

This review prepares the path to examine a novel and less-intensive approach of follow-up that could potentially replace the traditional methods, ultimately aiming to enhance survivorship outcomes, improve quality of life and reduce costs.

4) **What is the significance of new checklists?**

See lines 313-316

This symptom checklist is currently being tested for sensitivity and is used to trial a novel and less-intensive approach of surveillance that could potentially be used as an alternative to traditional surveillance method to detect recurrences as early as possible in endometrial cancer survivors.

5) **The manuscript just describes a review of other papers. Provide some guidelines to use the new symptom checklists.**

See response in Q1 above

6) **Figure 1: Provide more detail criteria for the screening (especially, the second and third screening). How is the second screening performed?**

See lines 187-191

In the first screen, abstracts of articles were reviewed against study eligibility criteria. Articles not meeting the study criteria were excluded, as were duplicate studies. The second screen involved review of full text articles by two independent assessors of which again, duplicate articles and those not meeting study criteria were removed. As a result, 12 retrospective studies were identified (Figure 1). Summary of study characteristics are presented in Table 1.

7) **Page 3 Line 3: Provide recent cancer statistics.**

See lines 75-80

Endometrial cancer is the sixth most common cancer in women worldwide and is the fourteenth most common cancer overall with 320,000 new cases diagnosed in 2012 (World Cancer Research Fund International, #210). A higher incidence of this cancer occurs in more developed countries with Northern America and Europe experiencing the highest incidence and Africa and Asia experiencing the lowest incidence (Ferlay, 2012 #210) however in 2008, more than half of deaths (64%) were in developing countries (Jemal A, 2011 #211).
Reviewer 2:

1) On page 3: The last sentence of the last paragraph should be part of the methods or should be reformulated into aims. Examining the follow-up scheme is not yet included in the aims.

See lines 124-135

The overall aim of this paper was to conduct a systematic review of relevant contemporary literature to comprehensively generate an updated list of symptoms potentially associated with a recurrence of endometrial cancer. Literature searches undertaken suggest indicate that controversies currently exist in regard to what constitutes effective surveillance management for endometrial cancer patients [Podczaski, 1992 #8]. This review explores alternative evidence based options to detect recurrences in women with endometrial cancer that will ultimately improve survival. Based on articles included in this review, this paper also explores the definition of endometrial cancer ‘recurrence’, determines recurrence rates in women with endometrial cancer, provides an overview of the leading symptoms of recurrence and identifies the post treatment surveillance schedules in these studies.

2) On page 4, I would recommend moving the first sentences of 'Study selection' and 'extraction of data' to the results section.

Thank you for your recommendation. The authors believe that it is appropriate for this information to be left in the current section, as information is easily accessible under the relevant headings and flows on to subsequent information.

3) Page 5: It is unclear that the paper would cover definition of recurrence. Please include in research questions or aims.

This has been included in study aims – see response to Q 1 above.

4) Page 6: Again, because the aims are not clearly formulated/don't cover 'recurrence rates', this section comes out of the blue.

This has been included in study aims – see response to Q 1

5) Tables 3 and 4 have quite some overlap, would it be possible to merge the tables?

Table 3 provides finding details on reported recurrence symptoms and provides details of findings such as combined occurrences and total occurrences/total symptomatic recurrences of studies combined (%)

Table 4 details recurrence symptoms that are listed in currently available symptom checklists and highlights symptoms that have found in this review (some of which are
not included in these checklist). Thank you for your suggestions however the authors feel that it is necessary to have these two tables listed separately in order to present information clearly.

6) Page 7: see point 1, examining the follow-up scheme is not yet included in the research aims.

This has been included in study aims – see response to Q 1 above

7) Page 7, first paragraph: The authors included many new symptoms, however, most of them only occur in a small portion of the patients with recurrences. Please describe in more detail.

See lines 257-260

Some of these additional symptoms found in this paper occurred in small numbers when studies reviewed in this paper were combined; these symptoms include fever, cardiac arrhythmia and urethral lesion.

8) Page 7/8: The authors state that patients should be educated on possible recurrence symptoms. Do the authors recommend to provide information on all 38 items? Patients generally have trouble recalling information given (McGuire 1996; Kessels 2003), and there has been research showing that patients tend to experience events they were warned about (Colagiuri et al 2012).

Thank you for your feedback.
See lines 289-294

Given the high symptomatic recurrence rate, educating survivors on commonly occurring symptoms that may indicate recurrence such as vaginal bleeding, pain, abdominal discomfort/swelling is crucial and could complement surveillance care. It is recommended that health professionals use their discretion in determining appropriate symptom recurrence information to provide to individual cancer survivors, and remind patients to promptly seek professional advice if any symptoms are experienced or concerns arise.

9) Page 8, second paragraph: The authors mention colorectal cancer, however, no references are given for this cancer type.

This has been deleted from the paper

Reviewer 3:

1) The two first sentences of the “objective” should be better formulated, what does “This is based on little evidence and alternative models need to be investigated” mean?

See lines 21-27
Objective: Women treated for endometrial cancer commonly attend clinic-based follow-up for up to five years even though there is evidence of discrepancies on effectiveness of this approach to improve survival. Furthermore, recent guidelines recommend patient education be the cornerstone for follow-up practices rather than clinical investigations such as medical imaging and tumour markers as prompt and thorough investigations of symptoms are more likely to improve survival. This current practice is based on little evidence and thus alternative models need to be investigated.

2) **Introduction should have more updated refs to cancer incidence, deaths and rank among cancers.**

See lines 75-80

Endometrial cancer is the sixth most common cancer in women worldwide and is the fourteenth most common cancer overall with 320,000 new cases diagnosed in 2012 (World Cancer Research Fund International, #210). A higher incidence of this cancer occurs in more developed countries with Northern America and Europe experiencing the highest incidence and Africa and Asia experiencing the lowest incidence (Ferlay, 2012 #210) however in 2008, more than half of deaths (64%) were in developing countries (Jemal A, 2011 #211).

3) **There should also be a description of the recurrence rate in general for EC, with the distinction in more/less developed countries. Also, the basic features of EC types and clinical assessment would be natural.**

See lines 76-80

A higher incidence of this cancer occurs in more developed countries with Northern America and Europe experiencing the highest incidence and Africa and Asia experiencing the lowest incidence (Ferlay, 2012 #210) however in 2008, more than half of deaths (64%) were in developing countries (Jemal A, 2011 #211).

See lines 92-96

Overall 13% of patients will develop recurrence (Fung-Kee-Fung, 2006 #4) with the highest risk within the first three years after primary treatment (Ueda, 2010 #2; Fung-Kee-Fung, 2006 #4; Gordon, 1997 #164); however cancer survival is lower in less developed countries due to a range of factors including lack of access to treatment (W, 2008 #215), lack of resources (Reeler A, 2009 #217) and economic disadvantage (Pinotti JA, 1984 #216).

See lines 82-87

There are various types of endometrial cancer, the most common being adenocarcinomas (tumors that begin in glandular cells) (Cancer Australia, #213). Other types of endometrial cancers include adenosquamous carcinoma, serous carcinoma and clear cell carcinoma, which are typically more aggressive forms of cancer (Cancer Australia, #213). Tests to detect endometrial cancers typically include physical examination, transvaginal ultrasound, hysteroscopy and biopsy, computerised tomography (CT), and magnetic resonance imaging (MRI) scans (Vistad, 2012 #98).
4) **Key word search term used are not intuitive; or combination (or not)?**

Key search terms used are as described in the article. The terms used were derived from research staff and previous search terms used in published articles on topic.

5) **References included in tables should be marked with corresponding number in ref-list.**

Added

6) **To what sites do the recurrences occur? And is there a correlation between sites and type of symptom? This would be appropriate to include in the paper.**

This review focuses on the need to explore alternative models of care in the follow-up of women with endometrial cancer, more specifically, the use of an updated symptom checklist to detect recurrences in women with endometrial cancer. This paper intentionally does not address specific sites of recurrences as we have previously identified several publications that are readily available that address this topic. Furthermore, several of the 12 articles included in this review do not provide sufficient details for this topic to be adequately addressed.

7) **It would also be of interesting if the authors would comment on the recurrence rates identified by symptoms in table 2, e.g Salvesen with 91% hit on recurrence by symptoms and Reddocks 41%. Is this related to the symptoms checklist within these papers?**

See lines 277-287

In this study, on average, symptomatic recurrence rates were lower in studies that included stage 1 participants only (58%) compared to studies that included stage 1-2 (81%), stage 1-3 (68%) or all stages (67%). Further studies need to be conducted to determine whether women with lower grades of endometrial cancer have less symptomatic recurrences compared to those with more advanced cancers. It may also suggest that women with lower grade cancers experience recurrence symptoms but these may not have significant impact on their life/lifestyle. For example, little/intermittent pain experienced and/or minor/intermittent/vaginal bleeding compared to symptomatic recurrences that occur in women with more advanced cancers, whom may experience more severe pain and/or heavy vaginal bleeding. This may result in women with lower grade cancer under-reporting recurrence symptoms. However, as stated above, further investigation is required prior to reaching clear conclusions.

If you have any further questions, please contact Monika Janda on m.janda@qut.edu.au
We look forward to hearing back from you

Regards,
Monika Janda