

ANSWERING REVIEWER

2013-12-05

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 6126-review.doc).

Title: Synchronous colorectal cancer: clinical, pathological and molecular implications.

Author: Alfred King-Yin Lam, Sally Sze-yan Chan, Melissa Leung

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6126

Thank you for your invitation for submission and comments of the reviewers, we are happy to revise the articles according to the comments of the reviewers. The followings are comments of the reviewers and my reply. In addition, we have made changes according to the guidelines of the editor with reference to the format suggested.

1. Response to Reviewer received on 2012-10-18 - 02444978

COMMENTS: This review addresses the problem of synchronous colorectal cancer by considering a large number of articles in the literature: it could be useful to describe what were the criteria for the selection of the articles, and possibly to add a table with the characteristics of the population for each study considered.

Despite the completeness of the aspects addressed, the overall impression is that this review represents a general introduction to the clinical and pathogenetic problems of synchronous colorectal cancer, that are illustrated in a simplistic way avoiding a more thorough analysis. The epidemiological aspects are described in a short and simplified way. The molecular aspects are treated without entering into a discussion of the molecular mechanisms. Finally, some aspects concerning the prognosis are reported: it could be useful to report more data on the follow-up.

The English language needs a comprehensive revision. The text appears unclear in many parts, shows clear errors and should be revised by a native English speaker.

RESPONSE:

The criteria of the selection of series were addressed in more details in the paragraph of the "Data collection".

A table, Table 1, was added to address the characteristics and follow-up data of all the series. In fact, detailed analysis including statically analysis was done before putting the conclusion and details were presented under every heading of the manuscript.

Two more paragraphs of the molecular mechanisms and findings were added under the section of "Molecular biology"

We have reviewed and tightened the English of the manuscript. The second author is a native English speaker. We have asked another native English speaker, Sharon Philips, in the revision and thanked her in the acknowledgement.

2. Response to Reviewer received on 2013-10-21 00050564

COMMENTS: *This is an important and timely review of the synchronous colorectal cancer. Though authors have covered most of the points but still they need to expand a little on each topic they covered. In a review article of this nature, consider using more graphs and tables to summarise the salient points of key/landmark studies. come up with your own "expert opinion" - you need to be able to give concrete and practical recommendations to the busy clinician reading this paper on basis of synchronous colorectal cancer Some more references need to added like : 1. Iain Ewing, Joanna J Hurley², Eleni Josephides³, Andrew Millar¹. The molecular genetics of colorectal cancer Frontline Gastro 2013;0:2013 flgastro-2013-100329v1-flgastro-2013-100329 2. Shuji Ogino*, Ajay Goel?. Molecular Classification and Correlates in Colorectal Cancer. The Journal of Molecular Diagnostics. Volume 10, Issue 1, January 2008, Pages 13–27 3. Colin C Pritchard¹, William M Grady². Colorectal cancer molecular biology moves into clinical practice. Gut 2011;60:116-129 Format of all reference should be same as pattern of reference no 9 is different*

RESPONSE:

Table 1 was added to summarize the findings of the series reported in the literature Additional references and comments were added in the section of "Molecular biology" as suggested

The format of the references and were re-checked to make sure they are present in uniform.

3. Response to Reviewer on 2013-11-17- 02462018

COMMENTS:

1. *This review does not address much the clinical aspects of synchronous colorectal cancers. Most of the issues that authors refer to as "clinical" are actually epidemiological aspects. Important clinical issues would be how to detect synchronous lesions preoperatively (in particular, the role of recent imaging such as CT colonography), how to treat them (please see comment #7), and how to follow the patients postsurgically. Up-to-date knowledge on these topic would require inputs from colorectal surgeons (maybe, also from gastroenterologists). It appears that none of them are included in the authors.*

2. *Although it is a narrative review, as authors tried to provide some summary data in a systematic review-like fashion using PubMed search (ref #1-57), it would be better to explain the specific details of the search strategy including exact search query, keywords, article eligibility criteria, and how they screened the search results for relevant articles. Systematic review-type summary data are generally considered more highly than narrative summary and, therefore, it is important to verify a bit more strictly the validity and reproducibility of the data.*

3. *For any specific data presented, indicate their sources by directly quoting the source articles in the sentence. This is particularly important for any pooled data. For example, in the last sentence of page 4-Introduction "Also, pooling the data from the series, the overall prevalence of synchronous colorectal carcinoma is 3.5% (3,582 of 102,725) of colorectal cancers", it is unstated which articles exactly authors pooled from. Similar loose citations are found in multiple areas throughout the manuscript, which should all be revised.*

4. *The last 2 sentences of the section entitled "Location of synchronous cancers" -- "Some authors reported that many.....examinations of synchronous colorectal cancers" -- appear to send contradicting messages. Please clarify.*

5. The "Pathology" section is confusing and it is difficult to grasp the key message. Moreover, the remarks regarding mucinous carcinoma mostly do not seem clinically relevant. I would recommend deleting all the discussion regarding mucinous carcinoma.

6. In some comparative data/statements presented, the reference for the comparison is missing. For example, in the 2nd sentence of the "Pathology" section, slightly more common compared with what patient group? These should be noted and revised throughout the manuscript.

7. The management part is too brief and appears outdated. I am not quite sure if "extensive operation such as subtotal colectomy is strongly advocated" is true. First, the quoted article (ref #12) is already 20 years old. Please review the current practice guidelines for colorectal cancer thoroughly and make necessary updates. An extensive surgery would be needed particularly for FAP and Lynch syndrome. However, other cases (authors stated that these "other" patients accounted for approximately 90%) may not need an extensive surgery. In fact, many such patients are currently treated with surgical resection plus colonoscopic management or dual colon resection. Colonoscopic resection (EMR and ESD) of early-stage colorectal cancers has recently been improved/adopted widely and plays an important role in the management of colorectal cancer.

RESPONSE:

1. The clinical aspect as suggested was added in the two paragraph in "Management" section of the manuscript. Please refer to point 7. Expert opinions were obtained from radiologist and surgeon before the revision

2. The specific details of the systemic review were added in a special paragraph "Data Collection"

3. The sources of the pooled data were added as references. We are pooling up all the data of the individual series in which the data are available.

4. In the last 2 sentences of the "Location of synchronous cancers", we have a typing mistakes and it is now fixed. The meaning is -- although some tumours occur very close, a large portion occur quite apart.

5. In the "Pathology" section, mucinous carcinoma is a feature of HNPCC which in turn is a risk factor for synchronous carcinoma and metachronous carcinoma in colon. The link was elaborated more in the edited manuscript.

6. In "Pathology", there is typing mistake in the second sentence and it is now fixed. These aspect of comparison have been looked after again and reviewed throughout the manuscript

7. Thank you for the advice and we have revisited the topics on "Management" along the lines suggested by the reviewer and confirmed the management with our surgical colleagues.

Review comment

This article is clear and comprehensive, few modifications are requested.

(1) A table resuming all the characteristics of synchronous colorectal cancer compared to solitary cancer is warranted.

(2) The separation of the conclusion from the management.

(3) The conclusion should include a clear proposition for similar cases management

RESPONSE:

(1) Table 1 is added as suggested

(2) The separation of the conclusion from the management is made. The final paragraph became 2 clear paragraphs

(3) The conclusion has a clear proposition for similar cases management

A handwritten signature in black ink, appearing to be 'Alfred Lam', with a stylized, flowing script.

Prof. Alfred Lam
Foundation Chair Professor and Head of Pathology
Griffith Medical School