PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The assessment and impact of sarcopenia in lung cancer: a systematic literature review.
AUTHORS	Collins, Jemima; Noble, Simon; Chester, John; Coles, Bernadette; Byrne, Anthony

VERSION 1 - REVIEW

REVIEWER	Rachel Murphy, Postdoctoral Fellow, National Institute on Aging, United States No competing interests to disclose.
REVIEW RETURNED	26-Aug-2013

THE STUDY	Add the reference: Winter et al. Normal protein anabolic response to hyperaminoacidemia in insulin-resistant patients with lung cancer cachexia. Clin Nutr 2012 31(5):765-73 and Martin et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 2013 31(12):1539-47.
RESULTS & CONCLUSIONS	The Tables should be presented in similar formats
GENERAL COMMENTS	This systematic review aims to inform readers of factors associated with loss of muscle mass and function in lung cancer. Overall, the topic is interesting and timely given de-conditioning in the general population and the increased number of older cancer patients. I have several general and specific comments. Introduction: why report the number of lung cancer diagnoses in the UK only when the studies in the systematic review are worldwide? In the Introduction the authors focus on NSCLC but in the tables and search terms, all lung tumor types are included. It is therefore unclear why the introduction focuses on NSCLC. Is it that studies in other tumor types are lacking? As it reads now, it sounds like sarcopenia/cachexia is only a problem in NSCLC. The introduction borrows quite heavily from Cruz-Jentoft et al. Sarcopenia: European consensus on definition and diagnosis. I would encourage the offers to offer a more original introduction to the topic rather than a re-hash of concepts that have been published. In addition a discussion on the methodologies used to measure lean body mass is needed; the paragraph on Page 28, line 5-12 should come before the tables. It is difficult otherwise to examine Table 2 and have an appreciation of how to reconcile these studies which vary widely in the assessment methods of lean body mass. The need for a focus on lung cancer and why sarcopenia criteria should be examined for a specific cancer type is unclear to me. The

	authors point out that 47% of lung cancer patients present with sarcopenia but this is not put into context with other tumor groups and the age of patients is also not mentioned. Therefore there is no indication of whether this is high or low prevalence. The Tables should be presented in similar formats. Ie. Table 2 with patients, tumor stage, method of measurement etc. It is unclear what studies in Table 2 are only in lung cancer vs. mixed tumor types and if the Results are relevant to the lung cancer patients or are general to the entire tumor groups studied. The P column is unnecessary since the authors indicate the significance in the Results column. In Table 2 define SMA at L3 Table 3: Some of the studies listed do not explore factors associated with muscle loss but rather are descriptive studies that belong in Table 2. ie. Baracos 2010, Prado et al. 2008 which assessed an outcome of muscle loss Add the references: Winter et al. Normal protein anabolic response to hyperaminoacidemia in insulin-resistant patients with lung cancer cachexia. Clin Nutr 2012 31(5):765-73 and Martin et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 2013 31(12):1539-47. Throughout the text of the paper it is important to distinguish between sarcopenia which has been assessed with the muscle mass alone or according to the definition of muscle mass and strength. ie. Page 7 line 47, refers to studies which only assess muscle mass. It is also important to recognize that the studies identified in the review are relevant to sarcopenia but did not necessarily assess sarcopenia ie. some were more broadly related to muscle outcomes or cancer cachexia. Some reference to the sarcopenia prevalence in the general population would be of interest and help readers understand the context of the prevalence in cancer the authors mention

REVIEWER	VICKIE BARACOS UNIVERSITY OF ALBERTA, CANADA No competing Interests
REVIEW RETURNED	18-Sep-2013

GENERAL COMMENTS	What I perceived to be the overall message of this document is that oncologists treating lung cancer patients might well to give some thought to an organ that they do not often consider: skeletal muscle. The document itself is a literature review of a small number of very disparate pieces of work concerning patients affected by lung cancer and in which either some quantitative measure of the amount of skeletal muscle and were some output of muscle functioning was measured. I can conclude that lung cancer patients are affected by muscle wasting and loss of muscle function but that the implications with respect to clinical outcomes and patient quality of life, the mechanisms and the possibility of reversal, remain largely unknown.

	I'm inclined to concur with these authors in the sense that I also wish that oncologists would think about muscle for a variety of different reasons. However if I were trying to make that case I would probably not restrict myself to lung cancer, a tumor group for which data concerning skeletal muscle in any form is so thin on the ground. Everything said here also pertains to patients who have advanced malignancies any kind. Think that this manuscript could be written and the clear and focused if it were to be entirely defined around the terms muscle mass, muscle loss and muscle function. However the present version takes the reader into a maze of text concerning the respective definitions of cachexia and sarcopenia in the relationship which might exist between them. There are current debates as to what are the diagnostic criteria and definitions of these terms that I find it of no interest to couch the main aim of this review in an extensive and inconclusive ramble about what is cachexia and what is sarcopenia. The authors gotten so involved in doing that that they fail to pay attention to more salient topics directly related to the purpose of the review. For example several different measurements of muscle mass are presented here without clearly explaining that some of the methods include: · upper arm muscle circumference, and anthropometric approach which is extremely crude, has considerable interobserver variation and lacks sensitivity to detect change over time. These measures are obviously specific to the musculature of the upper arm. · Diagnostic imaging-based approaches including dual energy x-ray, computed tomography, and magnetic resonance imaging, are considered gold standards for precision in the quantification of muscle and its change over time. Here again individual studies focus on a specific body part and it is of importance to note that appendicular skeletal muscle is measured using dual energy x-ray whereas most of the results that have been published using computed tomography or magnetic resonance imaging concern muscles on muscles of the legs. · Other approaches cited here are measures not of muscle mass but of whole body lean body mass (bioelectrical impedance, some DEXA results reported in this form, total body potassium) and this has the considerable caveat of including the masses of all the organs and of the cancer and its metastases and this lack of specificity is a real confounder the use of these approaches. If the target audience of this article is oncologists, then the authors would do well to give them very clear statement concerning these methods and it would seem to me to be quite important to indicate to them which the method of choice. Indeed since lung cancer patients usually have computed tomography images in their clinical record as these are used to follow the cancer over time, and because CT-based measures are considered gold standard and body composition research, this is the obvious way to go. With respect to the discussion of uncertainty as to the correct cut offs to define sarcopenia in patients with cancer, I suggest that the authors really read very carefully what is said about that in reference number 20 as well as in a new publication by Martin et al. 2013, cited below. One of the "key messages" of this paper concerns the heterogeneity of cutoff values for cancer related sarcopenia. This

	point really isn't explained in the body of the text were in the data presentation of this paper. Do we need cut-offs based on thoracic CT scans if lung cancer patients do not always have lumbar images? The following 3 articles can be usefully added to this presentation as they concern muscle wasting and sarcopenia in lung cancer patients. 2 of the publications are very recent and may have antedated the preparation of this manuscript. I'm not too sure why the search missed the 2007 article of Wieland which explores the relationship between a putative cancer derived proteolysis factor in muscle wasting in patients with non-small cell lung cancer. 1: Prado CM, Sawyer MB, Ghosh S, Lieffers JR, Esfandiari N, Antoun S, Baracos VE. Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? Am J Clin Nutr. 2013 Aug 21. [Epub ahead of print] PubMed PMID: 23966429. 2: Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, Murphy R, Ghosh S, Sawyer MB, Baracos VE. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013 Apr 20;31(12):1539-47. doi: 10.1200/JCO.2012.45.2722. Epub 2013 Mar 25. PubMed PMID: 23530101. 3: Wieland BM, Stewart GD, Skipworth RJ, Sangster K, Fearon KC, Ross JA, Reiman TJ, Easaw J, Mourtzakis M, Kumar V, Pak BJ, Calder K, Filippatos G, Kremastinos DT, Palcic M, Baracos VE. Is there a human homologue to the murine proteolysis-inducing factor? Clin Cancer Res. 2007 Sep 1;13(17):4984-92. PubMed PMID: 17785548. Believe that the content of table 2 is entirely redundant with the content of the subsequent tables which gives this information in full and that it should be deleted

VERSION 1 – AUTHOR RESPONSE

In response to comments from Dr Murphy

• We have added the references by Winter et al 2012, and Martin et al 2013, as suggested.

• In the introduction, we have omitted the UK-wide incidence of lung cancer, and included a worldwide incidence instead.

• With regards to referring to NSCLC in the introduction, we have revised this section to give a more general overview of sarcopenia in cancer. In our revised manuscript (last paragraph of the introduction section), we explain that we focus on lung cancer since it is a common condition, where sarcopenia is known to be prevalent and has a significant prognostic impact. However, we also include studies with participants with other cancer diagnoses, as made clear in the Methods section, under the heading Paper Retrieval.

• Whilst we acknowledge that our original manuscript quoted heavily from the consensus statement from Cruz-Jentoft et al., we believe that the criteria for diagnosis of sarcopenia should be uniform across all patient groups, whether in oncology, geriatric, or more general populations – this we acknowledge is still a matter of debate, as the second reviewer observes. While the current understanding of sarcopenia in cancer is taken as purely muscle wasting, the consensus diagnosis in elderly care includes loss of muscle function as well, therefore we have incorporated both these variables in our review.

• In the revised introduction, we describe the most common methods for assessing muscle mass and

muscle function, as suggested.
• The paragraph previously on page 28 has been moved to before the tables, as suggested.
• The prevalence of sarcopenia in lung cancer is put into context by comparison to breast and colorectal cancer patients, as suggested.
• In our original manuscript, Table 2 was meant to give an overview of all the studies reported in Tables 3 and 4; however based on both reviewers comments we have decided to omit Table 2 completely from the revised manuscript. Therefore in the revised manuscript, what was Table 3 is now the new Table 2, and what was Table 4 is now the new Table 3.
• With regards to distinguishing between sarcopenia as defined by muscle mass alone or in conjunction with muscle function, we believe this was already covered in the original manuscript, page 28 lines 7-12: "In addition, where the studies in this review defined a patient group as having sarcopenia, they did so based on loss of muscle mass alone, without evaluation of muscle strength or performance. This needs to be borne in mind wherever the term sarcopenia is used throughout this review." None of the studies included in this review defined sarcopenia from a composite of both muscle mass and strength/performance, although some studies did assess both muscle mass and function in tandem (new Table 3).
• In the discussion section, under limitations of the review, we have acknowledged the importance of recognising that some studies identified, although relevant to sarcopenia, were more broadly related to cachexia or muscle outcomes in nutrition for example, and did not necessarily assess sarcopenia per se.
• In the revised Introduction we have now included a statement on the prevalence of sarcopenia in the general population, as suggested.

In response to comments from Prof Baracos
• With regard to the manuscript being clearer and more defined if written based around the terms muscle mass, muscle loss and muscle function, we would like to clarify that our original manuscript was written with these terms in mind (ref search terms in Table 1). Indeed, our intention was to make this review as inclusive as possible, to account for the studies whereby muscle mass or strength may be have been measured (without necessarily accounting for sarcopenia) in conjunction with causative factors or clinical implications.
• We acknowledge Prof Baracos' opinion that our original manuscript commented heavily on the interplay between cachexia and sarcopenia. While we have revised the introduction in line with her constructive advice, we believe it is important to place sarcopenia in the context of cachexia, specifically in light of the re-definition of cancer cachexia (Fearon et al, Lancet Oncol 2011; 12(5):489-95). Hence, we have retained a few key points regarding this both in the revised introduction and discussion sections.
• We have presented a brief summary of common methods of measuring muscle mass, and given a statement of preferred options, as suggested.
• With regards to the cut-offs of the definition of cancer related sarcopenia, we have revisited the paper quoted above by Fearon et al, and the paper by Martin et al, as suggested. As suggested in both these papers, there is still much heterogeneity in cut-off values for defining sarcopenia. This, we feel, is reflected in the current diversity of methods of measuring muscle mass and muscle function. Further refinement, uniformity and validation of methods employed, and a clear statement of cut-off values in cancer-related sarcopenia would be an interesting area for future research.
• We have incorporated the papers by Prado et al 2013, and Wieland et al 2007, in our review, as suggested.
• Lastly, we have omitted Table 2 of the original manuscript, as suggested.

We would also like to note in addition, that as the reviewers suggested the inclusion of a few papers in the review which antedated the previous systematic search, we have updated our search up to and including October 2013, and the numbers of citations, abstracts and papers quoted in Figure 1 therefore are inclusive of this extended search.

VERSION 2 – REVIEW

REVIEWER	Rachel Murphy National Institute on Aging, United States
REVIEW RETURNED	29-Nov-2013

GENERAL COMMENTS	The authors have carefully addressed the comments from the reviewers. I find the readability of the manuscript to be greatly improved Minor comment Page 6, suggest adding reference for “third lumbar vertebra which can be related to whole body muscle mass"