January 8th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6869-review.doc).

Title: Cachexia and pancreatic cancer - are there treatment options?

Author: Mueller TC, Burmeister MA, Bachmann J, Martignoni ME

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6869

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers 1-5 (details on the next page)

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours

Marc E Martignoni
Chirurgische Klinik und Poliklinik, Klinikum rechts der Isar,
Technische Universität München,
Ismaninger Strasse 22,
81675 Munich, Germany
Email: martignoni@tum.de
Telephone: +49-89-41405093
Fax: +49-89-41404870

REVIEWER 1 (02544216)

The present review is well written and structured in its composition. The authors discuss in detail the current treatment option to treat cachexia in pancreatic cancer patients, illustrating the basis for the development of new therapies. Furthermore, they specifically address the emerging pharmacological treatments and provide a lot of valid information including what kind of clinical studies have been performed or are currently in progress. The background and the cited literature is up-to-date and properly discussed, and the data of the main studies on cachexia are summarized appropriately. The author's views and suggestions are in line with the current literature in this complex field of research. In particular, one relevant conclusion is the need for multimodal treatments. The Authors might add among the references the study by Barber et al., A polymorphism of the interleukin-1 beta gene influences survival in pancreatic cancer. Br J Cancer. 2000 Dec;83(11):1443-7.

We thank the reviewer for the positive feedback and his suggestion and have added the suggested reference on page - 7 in the section "Cachexia in pancreatic cancer: incidence, impact on prognosis and outcome".

REVIEWER 2 (00057400)

Overall this is a well written, concise summary of the currently available therapies. The authors have provided a logical flow to the review and offer a step-wise approach to treating the cachectic pancreatic cancer patient. See comments attached. Dr. Mueller and colleagues provide a logical summary of the issues associated with cachexia in pancreatic cancer and review many of the options for treatment that are currently available or under investigation. It is overall well written and flows easily, but does have a few grammatical errors. Some concerns:

1. The tables and figures were not available and therefore not able to be reviewed.
We apologize; tables and figures were originally uploaded in a separate file, now we included them in the same document.

2. The authors use the phrase "in addition" twelve times in the article.
In the revised manuscript we have markedly reduced the phrase "in addition".

3. Page 5, second paragraph, second sentence begins "But"
Thank you, we rephrased the sentence.

4. Page 5, third paragraph – "70% of patients are primarily resectable at first presentation" – this is much too high. Most sources would state 10-20%. Perhaps citing a source would be beneficial here.
We thank the reviewer for this advice and corrected this misunderstanding. What we meant to say was that 70% of tumors that were classified as resectable pre-operatively are really resectable intra-operatively. In total, of course, only 10-20% of all patients have reseectable tumors at first presentation, we also added an additional reference.

5. Page 6 – there is not much information presented on parenteral nutrition, yet the authors allude towards
its usage in their multimodal therapy and stepwise approach. Perhaps expanding on the indications of it would be enlightening rather than simply referring to the ESPEN group guidelines.
We thank the reviewer for this advice and have added more information about the indications for parenteral nutrition in this paragraph (page 10).

6. Page 9, under appetite stimulation. The authors state there are significant side effects of cannabis extracts – it would be helpful to clarify the nature of these (similar to how the authors listed side effects of other medications throughout the article).
Thank you for this remark, the side effects of cannabis treatment, like somnolence and mental confusion were added in this section (page 13).

7. Page 12 – paragraph 4, "GIT cancers" are these GI cancers? Not GIST? Does this stand for gastrointestinal tumor cancers?
We are sorry, in German GIT cancers means gastrointestinal tract cancers, the abbreviation was corrected.

8. Page 16, second paragraph – if the authors are recommending parenteral nutrition as the next step, more information should be placed in their discussion on page 6. See comment #5. The large-scale meta-analysis cited in the paragraph was referring to ORAL nutritional interventions.

See answer to comment #5

9. Page 16, third paragraph, the authors recommend uniform screening for cachexia using CT to determine lean body mass. How easily do the authors think this can be implemented? Should surgical and medical oncologists be able to make this determination or should it be included in the radiologist's report? See Engelsbe, et al. Analytic Morphomics, Core Muscle Size, and Surgical Outcomes. Ann Surg 2012;256: 255–261

Thank you for this important question, more details are now given on the technique and the implantation in clinical practice.

Page 7: To perform the assessment, cross-sectional areas of the left and right psoas muscles at the level of the fourth vertebra can be used. The surface will be expressed in mm2 (ENGELSBE MJ 2010).

Page 21: Since this new technique is not a standard measurement in all CT scans today, and a specific software is required, an individual agreement with the radiologist should be defined.

10. Page 17, third paragraph. The first sentence is not a complete sentence.

Thank you, we rephrased the sentence.

11. Page 18, the paragraph describing ongoing trials might be better served under the sections of Pharmacologic Therapies, *emerging pharmacological therapies* and *combination protocols* and reserve the last section of the paper for final conclusions.

Thank you for this good suggestion, we moved the paragraph to the section "emerging pharmacological therapies."

Overall this is a well written, concise summary of the currently available therapies. The authors have provided a logical flow to the review and offer a step-wise approach to treating the cachectic pancreatic cancer patient. I would recommend accept with revision as noted above, pending approval of tables and figures.

REVIEWER 3 (02544961)

The authors presented a systemic review on cachexia in pancreatic cancer, the authors have summarized the recent definition of the mechanisms of cachexia in pancreatic cancer, as well as provided an integrative view of multiple treatment agents for cachexia. It contains indisputable logic, fluid organization and substantial content which merit publication, but there are still some problems that need to be solved.

1. **In section "Current treatment options of cachexia in pancreatic cancer patients", the author mentioned that "Approximately 70% of patients are primarily resectable at first presentation". Maybe the source of the cited article is needed, from my point of view, only 20% pancreatic cancer patients are diagnozed resectable.**

We thank the reviewer for this advice and corrected this misunderstanding. What we meant to say was that 70% of tumors that were classified as resectable pre-operatively are really resectable intra-operatively. In total, of course, only 10-20% of all patients have resectable tumors at first presentation, we also added an additional reference.

2. **In the same section, the author mentioned "Palliative treatment of non-resectable pancreatic cancer consists of chemotherapy and supportive care". Maybe radiotherapy is also a valuable optional therapeutic agent for these patients, especially those with severe pain.**

Thank you for this comment; we added radiotherapy as possible additional treatment option in palliative care, however in Germany this is not routinely practiced, but reserved for specific indications.

REVIEWER 4 (02545029)

In their current review, Muller et al. reviewed the clinically highly relevant issue of cancer cachexia, with particular emphasis on pancreatic cancer (PC)-associated cachexia. They provide an overview on the different definitions of cachexia and its prognostic impact in PC and lung cancer (NSCLC). Furthermore, they refer to the currently applied therapeutic approaches to cachexia and cite several trials which investigated several different pharmacological agents. Moreover, the step-up therapy approach that the authors propose for treating cachexia is very plausible. Overall, the study contains a good and comprehensive summary of therapeutic approaches to cachexia, and it effectively demonstrates how little we know about cachexia and how little we probably do to treat it. In this well-written review, I feel that two major points are missing:

1. It seems that the pro-inflammatory milieu that is generated during cancer as a complex disease, and the mixture of humoral and metabolic changes in cancer contribute to cachexia. While the authors have discussed some of the humoral factors (e.g. cytokines), they did not refer to the specific metabolic changes that occur in these patients. What arms of the metabolism are affected by cancer? Lipid metabolism? Glucose metabolism? Protein metabolism?

Thank you for this interesting remark. In cachexia due to pancreatic cancer, all arms of metabolism are affected, especially glucose metabolism, which is also believed to enhance protein and lipid catabolism. We did not want to go into too much detail here, since this is a very complex field and a multitude of mediators is involved in these metabolic changes. Discussing all of them would certainly go beyond the bounds of this article, whose primary focus is the currently available therapy for cachexia in pancreatic cancer patients.

2. One major question is, how can doctors integrate assessment of cachexia into their daily practice? The authors state that cachexia is associated with worse survival in pancreatic cancer. In this regard, every doctor dealing with PC or NSCLC should routinely monitor patients for cachexia. Is weighing the patient sufficient? Or should every CT scan of these patients be routinely used to monitor the thickness of the muscle and fat tissue, i.e. to obtain a musle mass/fat index? I think such an index and its implementation would allow objective monitoring of cachexia and the amelioration of cachexia and thus prognosis. But are there are difficulties in front of the implementation of such a measurement on a routine basis?

This is a very good question. In our opinion all cancer patients, especially pancreatic, gastrointestinal and lung cancer, should be regularly screened for cachexia. Weighing the patient is the basis of screening, but not sufficiently specific. Ideally screening and monitoring should be integrated in the CT-scans used for primary staging and monitoring of every patient. The screening and monitoring should be combined with weighing, evaluation of nutritional risk scores and dietary counseling. This is already described in our article, see page 21 last paragraph. The implementation of this screening in clinical routine is of course dependent on the setting and available resources at the hospital, but should not be too difficult to achieve, since weight is

routinely recorded on admission and the standard evaluation of nutritional risk scores does not require a lot of additional work load. Moreover, most cancer patients also regularly have CT-scans for staging and follow-up. Once the software for calculating muscle/fat index is implemented, it would be easy to standardize and include it in the radiologists report, representing a very specific and sensitive parameter for the monitoring of cachexia.

Minor comments:

1. **Page 5, paragraph 3: the rate of resectable PC patients at first diagnosis is between 10-20%, and certainly not 70%. Please correct this together with an appropriate citation.**

We thank the reviewer for this advice and corrected this misunderstanding. What we meant to say was that 70% of tumors that were classified as resectable pre-operatively are really resectable intra-operatively. In total, of course, only 10-20% of all patients have reseectable tumors at first presentation, we also added an additional reference.

2. **Page 6, paragraph 1: The range of caloric intake (1000-1500 kcal) seems to be rather adequate for a non-cachectic, normal individual with little regular exercise. This range should be reconsidered to be somewhat higher (i.e. close to 2,000 kcal) in the revised manuscript, or at least a supporting reference with these values should be shown.**

Thank you for this remark. The source we cited is Morely J, Calories and cachexia, Current Opinion in Clinical Nutrition and Metabolic Care 2009, 12:607–610, a detailed article on caloric supplementation of cachexia patients." Maintenance of caloric intake is essential to survival. There is general consensus that persons with cachexia should receive between 1000 and 1500 calories a day."
In the ESPEN guidelines it is written: „Total daily energy expenditure in cancer patients may be assumed to be similar to healthy subjects, or 20–25 kcal/kg/day for bedridden and 25–30 kcal/kg/day for ambulatory patients". So for a patient of 60kg, this would be between 1200 and 1800 kcal/kg/day.

3. I unfortunately could not locate the Figure files, so I would kindly ask for their re-upload in the revised version.
We apologize; tables and figures were originally uploaded in a separate file, now we included them in the same document.

REVIEWER 5 (02545004)

This is an interesting and well written review article on cachexia and pancreatic cancer. Authors give an overview of current therapies, propose a stepwise approach for clinical practice after having well described diagnostic criteria and precisely define cachexia. There are several points to increase the quality of this review:

1. Authors should define precisely what they mean in terms of "pancreatic cancer" in the background section "Cachexia in pancreatic cancer", ie. Pancreatic Ductal Adenocarcinoma only (as ADK is only mentioned at the end of the manuscript in page 18) or do they include other types of pancreatic cancers?

Thank you, the term pancreatic cancer refers mainly to pancreatic ductal adenocarcinoma. Unfortunately, most of the cited clinical trials do not specify if they included other types of malignant pancreatic neoplasms in their studies. However, app. 95% of pancreatic neoplasms are adeno-carcinomas so that is what is usually meant by pancreatic cancer. We added this to the background section.

2. The part: "Cachexia in pancreatic cancer: incidence, impact on prognosis and outcome" (starts at page 4) should be enriched. For example, in the section at the end of page 4, authors could described more precisely what are "other stimulators" of catabolic pathways as well as "catabolic" and "anabolic pathways" in order to describe what is known about alterations in metabolism in pancreatic cancer. Same for neuroendocrine hormones and tumor-derived factors (page 5), authors should shortly describe them.

We did not want to go into too much detail here, since this is a very complex field and a multitude of mediators is involved. Discussing all of them would certainly go beyond the bounds of this article, whose primary focus ist the currently available therapy options for cachexia in pancreatic cancer patients.

3. Authors should define the "acute phase response in the liver" in the context of cachexia (end page 4)

Thank you for this suggestion, also here we did not want to discuss the complex molecular mechanisms that lead to cachexia in too much detail. However, we added some more information about the role of the liver and the inflammatory response in this paragraph.

4. Page 5: "70% of patients are primarily resectable at first presentation": this is not what it is usually considered, authors should mention a reference or correct the percentage.

We thank the reviewer for this advice and corrected this misunderstanding. What we meant to say was that 70% of tumors that were classified as resectable pre-operatively are really resectable intra-operatively. In total, of course, only 10-20% of all patients have reseectable tumors at first presentation, we also added an additional reference.

5. Page 9 authors have to explain the side effects of the use of cannabis extract.

Thank you for this remark, the side effects of cannabis treatment, like somnolence and mental confusion were added in this section (page 13).

6. In the part "pharmacological treatment of cachexia in pancreatic cancer patient",
- It is not always properly mentioned if clinical trials have been done on pancreatic cancer or on other types of tumors (excluded pancreatic cancer).
Thank you for this good comment, we revised the clinical trials and added this information where it was possible.

- Authors should invert the parts "anti-cytokine strategies" and "anti-inflammatory drugs" to fit with Table2.
Thank you, we inverted the two parts.

- Authors have to include Figure and Table legends in the manuscript.
We apologize; tables and figures were originally uploaded in a separate file, now we included them in the same document.

Minor points:
- Reference 21 is not properly cited (it was published on February 2013 and not an "advance online publication").
Thank you the citation was corrected.

- Table 1: typo correction: Acetyl-coA.
Thank you, we corrected this typo.

- Figure 2: Authors could play with colors to better highlight parts/columns in Figure 2 ("Supportive therapy" can be in a different color than the rest of the figure).
Thank you for this suggestion, we slightly changed figure 2 to make it clearer.

- Not all abbreviations are explained.
Thank you we went through all abbreviations and explained where missing.