

PEER REVIEW HISTORY

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ARTICLE DETAILS

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| TITLE (PROVISIONAL) | A randomized controlled trial testing the feasibility of an exercise and nutrition intervention for ovarian cancer patients during and after first-line chemotherapy (BENITA-study) |
| AUTHORS | Maurer, Tabea; Belau, Matthias; von Grundherr, Julia; Schlemmer, Zoe; Patra, Stefan; Becher, Heiko; Schulz, Karl-Heinz; Zyriax, Birgit-Christiane; Schmalfeldt, Barbara; Chang-Claude, Jenny |

VERSION 1 – REVIEW

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| REVIEWER | Lopez, Pedro Edith Cowan University School of Medical and Health Sciences |
| REVIEW RETURNED | 06-Aug-2021 |

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| GENERAL COMMENTS | <p>completion rate and adverse events were primary outcomes. Secondary outcomes were efficacy endpoints such as quality of life, fatigue, objectively physical function measures and dietary intake and quality. In summary, the trial is interesting and important to determine the feasibility of lifestyle interventions such as exercise and nutrition in a population requiring additional studies. Furthermore, the study design is adequate considering the treatment side-effects and current knowledge in other cancer populations. However, some major points need to be addressed:</p> <p>1) Introduction – The authors brought two important concepts for this group of cancer patients: frailty and cancer cachexia. The rationale of the study in terms of outcomes and interventions is linked to muscle loss and malnutrition. However, the concept and definition of frailty, cachexia and sarcopenia overlap each other. It is important to define all these in the introduction and make sure that although they are not the same, an intervention comprising exercise and nutrition can reduce the risk for all of them.</p> <p>2) Intervention – It is described throughout the text that a “combined exercise and nutrition intervention” comprising endurance, resistance and balance exercises was the intervention in question. However, there is a lack of specific information about frequency, prescribed exercises, exercise volume and intensity, and if it was supervised or not (even that it says “home-based”, that does not mean “unsupervised home-based”). The authors should indicate how the intervention was conducted; otherwise, the feasibility aspect of the study becomes unclear (“feasibility of what?”).</p> <p>3) Intervention - I am a bit concerned about the endurance component of the exercise program. If the authors built the rationale around frailty, cachexia and sarcopenia, and the catabolic effects from chemotherapy, why prescribe aerobic exercise? I suggest the authors read the last ESSA position statement in cancer management (Hayes et al. Journal of Science and Medicine in Sport, 2019; doi: 10.1016/j.jsams.2019.05.003) as well</p> |
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as the last ACSM international roundtable (Campbell et al. MSSE, 2019; doi: 10.1249/MSS.0000000000002116) to address this issue and support the intervention prescribed. Exercise should be specific and tailored to improve the outcome of interest. Also, I recommend the authors inform the volume of endurance and resistance exercise prescribed.

4) Intervention – Same as above for the nutritional intervention. What was the method to increase protein and calorie intake? Was this done by using protein supplementation, or increasing the size of meal portions? Several methods are able to produce the same result, however, they need to be defined in this study.

5) Procedure – The authors should write the statistical methods in a separate subsection.

6) Measures – Adherence to the exercise intervention was defined as the ratio of planned and completed interventions. How this was defined? The authors are referring to exercise sessions attended, or exercise dosage completed? This needs to be clear.

7) Measures – Adherence to the nutrition intervention was defined as changes in protein and caloric intake. As above, how this was defined? There is a cut-off value to say that patients adhered or not?

8) Methods and Results – The lack of outcomes such as body weight (or BMI) or body composition (or a measure indicating whether the intervention could maintain muscle mass) is a limitation. Considering that the rationale was to counteract the catabolic side effects from chemotherapy, presenting these measures would improve the study. Furthermore, as abovementioned, frailty, cachexia and sarcopenia rely on some similar characteristics. Providing results such as body weight or body composition could show that, besides being feasible, exercise + nutrition can potentially prevent these treatment-related side effects in women with ovarian cancer.

9) Results – The feasibility outcomes and efficacy endpoints are reported in the results section. Why do not perform statistical analysis for the efficacy endpoints (physical function, QoL...)? These outcomes are also important and associated with clinical endpoints such as survival, cardiovascular and metabolic comorbidities. I understand that this is a pilot study and, maybe, the power necessary to find differences in those measures may not be enough. However, this is a very important opportunity for future directions as well as demonstrate if exercise + nutrition can alleviate treatment-related side effects.

10) Discussion – A first paragraph of “summary of findings” may improve the reading well. Please, provide 3-4 main findings of the study to help the reader understand the importance of this study.

11) Limitations – In the ‘strength and limitations’ section, the authors stated, “A blinded randomisation process was not possible due to the study design”. What specifically the authors mean by that? Is it about concealed allocation, blinding of study assessors or blinding of the intervention? In addition, it is stated in the ‘Procedure’ sections, “Group allocation was performed by a statistician not involved in data collection.”. So, this is very unclear, and I suggest the authors rewrite this bullet point. Finally, if not able to provide a measure of body weight or body composition, this should be treated as a limitation of the study.

Specific comments:

1) Abstract, Objectives, ‘[...] serious disease’ – severe or any other word may work better. All diseases are sort of ‘serious’.

2) Introduction, page 4, lines 11-17 – Please, provide a reference.

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| | <p>3) Introduction, page 4, lines 16-27 – The sentence is a bit confusing. Could the authors rephrase?</p> <p>4) Introduction, page 4, lines 25-27 – “Exercise equivalent”?</p> <p>5) Introduction, page 4, lines 25-29 – “Cardiopulmonary fitness” is not so common. I suggest change to ‘cardiorespiratory fitness’.</p> <p>6) Introduction, page 4, lines 28-34 – “[...] significantly improved HRQoL”. The study in question did not show improvements but a significant positive association between higher physical activity levels and quality of life. Please, amend the sentence.</p> <p>7) Introduction, page 4, lines 47-49 – “Yet, Randomized controlled trials...”. Randomised should be lower-case.</p> <p>8) Introduction, page 4, lines 50-52 – “[...] bimodal intervention”. Better expand to ‘exercise and nutrition interventions’ rather than bimodal.</p> <p>9) Introduction, page 5, lines 15-17 – “[...] in-person assessments” What do the authors mean by this? I would recommend rephrasing the sentence in question.</p> <p>10) Measures, page 7, lines 56-60 – Please, remove the first bracket of ‘(1)’ and ‘(2)’ since the references are in the same style.</p> <p>11) Results, page 9, lines 13-17 – “The majority (73.3%) of patients was diagnosed as having advance stage disease”. Please, specify that this refers to stage III and IV patients.</p> <p>12) Table 1 and results section – Sports or sports interventions? What does that mean? Do the authors are referring to physical activity levels or exercise sessions? Please, clarify throughout the text.</p> <p>13) Results, page 11, lines 48-52 – Please, remove this first sentence. This was already informed in the methods section.</p> <p>14) Results – Where is the nutritional information for the control group? This should also be informed.</p> <p>15) Results – Please, see my comment about statistical analysis above (point 9).</p> <p>16) Discussion – Please, see my comment about the first paragraph of the discussion (point 10).</p> <p>17) Discussion, page 16, lines 42-44 – “[...] rates of 70 – 100 stated a recent review” stated in a recent review.</p> <p>18) Discussion, page 17, lines 3-4 – “by previous studies (10)” but is only one study.</p> <p>19) Discussion – Please, remember to adequate the discussion section accordingly to the results after informing statistical differences between groups.</p> |
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| REVIEWER | Cartmel, Brenda Yale University School of Public Health |
| REVIEW RETURNED | 01-Nov-2021 |

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| GENERAL COMMENTS | <p>The manuscript describes the results of a feasibility study of a 12-month exercise and nutrition intervention for ovarian cancer patients initiated during first-line chemotherapy.</p> <p>Comments to the author:</p> <p>a) Line 48: ‘randomized’ the ‘r’ should not be capitalized.</p> <p>b) Page 7, line 40: ‘study coordination’ I believe should read ‘study coordinator’.</p> <p>c) Page 7, line 42: Can the authors clarify, if the study coordinator conducted the baseline assessment and if so, when the study coordinator became aware of the group allocation for each patient? As currently written, it appears it was prior to the baseline assessment.</p> <p>d) Page 7, line 53: reference 16 is duplicated.</p> |
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| | <p>e) In some instances, the physical activity intervention is referred to as the 'exercise' intervention (e.g., page 8, line 25 and in some instances the 'sports program' (e.g., page 9, line 18). Suggest keeping the wording consistent, 'exercise' seems more appropriate than 'Sports' (i.e., a definition of sport: 'an activity involving physical exertion and skill in which an individual or team competes against another or others for entertainment').</p> <p>f) In the paper the home-based training is described as including endurance, resistance and balance exercises (page 8, line 30). A more comprehensive description of the training is needed and doesn't appear to be provided as stated in reference 23. For example, is the endurance exercise predominantly walking? What are the resistance exercises that are recommended? Is the goal to do each of endurance, resistance and balance exercises every day?</p> <p>g) Similarly greater detail regarding the nutritional intervention is needed for in phase 1 (page 8, lines30-40). Was the goal to increase calorie intake in all patients? Was there a calorie goal based on initial weight, weight change during phase 1, initial calorie intake?</p> <p>h) Are any written/online instructions provided regarding the exercise and nutritional intervention page 8, line 25)?</p> <p>i) Can the authors quantify the reasons for refusal to participate in the study (page 9, line 46-48) and in the consort diagram? Is it possible to compare demographics and disease characteristics in those who were randomized to those who were eligible but chose not to participate in the study? This information would be helpful in knowing factors associated with participation e.g., are younger patients more likely to participate.</p> <p>j) Page 10, line 14; 'was' should be.</p> <p>k) Page 12, lines 3-8; The authors stated that all 15 participants completed T0 and T1 in line 3. However, in line 8, it is stated that 13 patients completed the T1 assessment. Please reconcile.</p> <p>l) Page 12, line 59 'a patient of the of the intervention group' - 'of' should read 'in'. Please check this though out the manuscript.</p> <p>m) Page 12, line 56: The calorie intake is reported in grams per day. This unit seems incorrect.</p> <p>n) Table 2: It is unclear what the data regarding the accelerometer refers to. Was the accelerometer used in the 6-minute walk test? Please clarify in the table, perhaps with a footnote. Similarly with the case report form. What data was collected via the case report form?</p> <p>o) Page 17, line 43; Missing '%' after 70-100.</p> <p>p) Page 18, line 50: 'lead' should be 'led'</p> <p>q) 'Allocation concealment mechanism' – it is stated that this is describe in the published study protocol (Ref 23), but I am unable to find this information.</p> |
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VERSION 1 – AUTHOR RESPONSE

Answers to Reviewer #1:

The authors are grateful for Dr. Lopez' constructive feedback and would like to thank him for his effort to enhance our work. We believe the changes made based on his comments have greatly improved the manuscript.

1) Introduction – The authors brought two important concepts for this group of cancer patients: frailty and cancer cachexia. The rationale of the study in terms of outcomes and interventions is linked to muscle loss and malnutrition. However, the concept and definition of frailty, cachexia and sarcopenia overlap each other. It is important to define all these in the introduction and make sure that although they are not the same, an intervention comprising exercise and nutrition can reduce the risk for all of them.

We agree, that all of these conditions share equal etiological factors and are therefore often concurrent in the same patient. We changed our introduction to better define these syndromes and to underline the importance of a multi modal intervention to tackle them simultaneously.

The Introduction now states on p. 5 l. 4 ff:

“Major side effects of ovarian cancer and its treatment are cancer cachexia, sarcopenia, frailty, and malnutrition. They all lead to either loss of skeletal muscle mass and/or fat mass of the patient and are associated with decreased health-related quality of life (HRQoL), cancer related fatigue (CRF) and poorer outcome (3, 4). As these syndromes share similar etiological factors such as reduced food intake, inflammation, hormonal changes, increased energy requirements and reduced physical activity (5) more than one condition can be present in the same patient at the same time. Hence, a combined intervention consisting of an exercise and nutrition program may be most successful to address these conditions in patients with advanced cancer (6, 7).”

2) Intervention – It is described throughout the text that a “combined exercise and nutrition intervention” comprising endurance, resistance and balance exercises was the intervention in question. However, there is a lack of specific information about frequency, prescribed exercises, exercise volume and intensity, and if it was supervised or not (even that it says “home-based”, that does not mean “unsupervised home-based”). The authors should indicate how the intervention was conducted; otherwise, the feasibility aspect of the study becomes unclear (“feasibility of what?”).

The exercise intervention was unsupervised and home-based. However patients were contacted once a week during phase I and every other week during phase II to tailor the program to the individual’s needs and explain new exercises that were added to the daily practice. During chemotherapy every third visit was in person to ensure that new exercises could be demonstrated if needed. After chemotherapy patients were offered personal visits if necessary, but were mainly contacted by telephone, assuming that they were used to their practice and familiar with the exercises and instructions. It was the aim of this study to prove (1) that exercise started early, i.e. during chemotherapy was safe, feasible and accepted in ovarian cancer patients. In other words, we aimed to show that patients were motivated to participate, adhered to the program and did not experience any adverse events linked to the intervention. It was not the aim of this study to prove the effectiveness of the program.

As patients’ ability to exercise was very different the individual programs tailored to each patient’s needs were very heterogeneous in terms of exercises type and intensity. Therefore our sport experts categorized exercises based on their type (balance, endurance, resistance) and their intensity and chose a combination of exercises that was well suited for each patient’s capabilities. Each patient received a personalized program, however all exercises were taken from this shared pre-defined pool of possible exercises and all patients were asked to train for 15-30 minutes daily.

We added the exercise catalogue from our program to the supplements and further explained the exercise intervention in the methods section:

p. 7, l. 13 “unsupervised home-based training”

P. 7, l. 15 ff: An exercise catalogue was developed by sports scientist and all exercises were categorized based on their intensity. Each patient received an individually adapted program consisting of exercises that are part of the catalogue. The program was adjusted each week (phase I) or every

other week (phase II) if needed based on the patients' individual abilities and current needs. Exercises using abdominal muscles were not included until full recovery from surgery. The exercise catalogue used to build the exercise programs can be found in the supplements.

3) Intervention - I am a bit concerned about the endurance component of the exercise program. If the authors built the rationale around frailty, cachexia and sarcopenia, and the catabolic effects from chemotherapy, why prescribe aerobic exercise? I suggest the authors read the last ESSA position statement in cancer management (Hayes et al. Journal of Science and Medicine in Sport, 2019; doi: 10.1016/j.jsams.2019.05.003) as well as the last ACSM international roundtable (Campbell et al. MSSE, 2019; doi: 10.1249/MSS.0000000000002116) to address this issue and support the intervention prescribed. Exercise should be specific and tailored to improve the outcome of interest. Also, I recommend the authors inform the volume of endurance and resistance exercise prescribed.

The volume of endurance and resistance exercises was tailored to the patient's abilities and needs. Hence, there was a great variability in programs prescribed depending on the patients' health and fitness. The main goal was to keep patients active to prevent them from becoming sedentary which is often observed in women after an ovarian cancer diagnosis.

In accordance, the German ovarian cancer patient guidelines recommend an exercise program consisting of endurance, flexibility and strength. Our exercise program was developed based on these recommendations and on sport experts' opinion. As the pilot phase is already completed we will not be able to change the exercise program based on your literature recommendation. We do however thank you for your feedback, as we find it very important, and will keep this valuable information in mind when moving into the main study.

4) Intervention – Same as above for the nutritional intervention. What was the method to increase protein and calorie intake? Was this done by using protein supplementation, or increasing the size of meal portions? Several methods are able to produce the same result, however, they need to be defined in this study.

We added the following information to the intervention section (p. 8, l. 22 ff):

“Patients who were in need of an increased calorie and protein intake were advised to consume several smaller meals throughout the day. Nutritionists recommended the use of oils and butter if necessary. Furthermore, patients were educated about suitable types of foods and drinks that are high in protein, fat or energy. If deemed necessary oral sip feeding was suggested. These recommendations were based on the patients development in weight as well as other body composition parameters derived from BIA measurements (e.g. phase angle, muscle mass).

5) Procedure – The authors should write the statistical methods in a separate subsection.

We added a section for statistical methods on page 9 line 11

“Statistical methods

Recruitment rate was defined as the ratio of patients eligible to participate and patients who signed informed consent. Completion rate was defined as the ratio of patients who signed informed consent and those who completed the 12 months intervention. General adherence to the intervention was defined as the ratio of planned and completed counseling sessions, adherence to the exercise program was further assessed using exercise diaries filled out every week until week 18 and once a months until 12 months follow-up. Adherence to the nutrition intervention in phase I was described in terms of changes in protein and caloric intake compared to baseline. During phase II adherence to the nutrition intervention was interpreted in terms of changes in MEDAS (Mediterranean Diet Adherence Screener) score points between T0 and T3 (25). Descriptive analyses were conducted for all

parameters assessed during the study. No inferential statistics were used as this feasibility trial was not powered for this purpose.”

6) Measures – Adherence to the exercise intervention was defined as the ratio of planned and completed interventions. How this was defined? The authors are referring to exercise sessions attended, or exercise dosage completed? This needs to be clear.

We used two measures to report adherence. The first was adherence to the consultation sessions that were either in-person or by phone call. The second measure was based on an exercise diary that patients were asked to fill out after each work-out session

We changed the following sentence (p.9, l. 14ff):

General adherence to the intervention was defined as the ratio of planned and completed counseling sessions. Adherence to the exercise program was further assessed using exercise diaries filled out every week until week 18 and once a month until 12 months follow-up.

7) Measures – Adherence to the nutrition intervention was defined as changes in protein and caloric intake. As above, how this was defined? There is a cut-off value to say that patients adhered or not?

We did not define a cut off, because the recommendation to increase protein and calorie intake was highly depending on the individual's needs. We chose to report calorie and protein intake as an additional parameter for intervention adherence, because adherence to the counselling sessions alone did not allow us to make assumptions on actual changes in lifestyle. We are however aware that these outcome measures are not without limitation.

8) Methods and Results – The lack of outcomes such as body weight (or BMI) or body composition (or a measure indicating whether the intervention could maintain muscle mass) is a limitation. Considering that the rationale was to counteract the catabolic side effects from chemotherapy, presenting these measures would improve the study. Furthermore, as abovementioned, frailty, cachexia and sarcopenia rely on some similar characteristics. Providing results such as body weight or body composition could show that, besides being feasible, exercise + nutrition can potentially prevent these treatment-related side effects in women with ovarian cancer.

BMI as well as body composition were measured throughout the trial. However, both BMI as well as body composition are strongly influenced by other factors (e.g. ascites, residual tumor) and interpretation of changes is limited. Furthermore, due to technical difficulties not all patients received BIA measurements at all time-points, therefore we chose not to report our findings. However, since this is a feasibility study, we do not think that these are limiting factors, because it was not the goal of the study to investigate the effectiveness of the intervention.

9) Results – The feasibility outcomes and efficacy endpoints are reported in the results section. Why do not perform statistical analysis for the efficacy endpoints (physical function, QoL...)? These outcomes are also important and associated with clinical endpoints such as survival, cardiovascular and metabolic comorbidities. I understand that this is a pilot study and, maybe, the power necessary to find differences in those measures may not be enough. However, this is a very important opportunity for future directions as well as demonstrate if exercise + nutrition can alleviate treatment-related side effects.

We agree that the efficacy endpoints are of great importance and are planning on conducting a major RCT. The main trial will analyse all outcomes in question. The feasibility study however, was not

sufficiently powered for the suggested analyses. Therefore, we chose to show changes in outcome measures in a descriptive way only.

10) Discussion – A first paragraph of “summary of findings” may improve the reading well. Please, provide 3-4 main findings of the study to help the reader understand the importance of this study.

We added a paragraph as suggested (p.17, l.1ff).

This pilot trial investigating the safety, acceptance and feasibility of a combined exercise and nutrition intervention during and after first-line chemotherapy in ovarian cancer patients demonstrated that patients were motivated to enroll and adhered to the program and in addition that an exercise and nutrition intervention as early as during chemotherapy was not associated with any adverse effects for this vulnerable patient group.

11) Limitations – In the ‘strength and limitations’ section, the authors stated, “A blinded randomisation process was not possible due to the study design”. What specifically the authors mean by that? Is it about concealed allocation, blinding of study assessors or blinding of the intervention? In addition, it is stated in the ‘Procedure’ sections, “Group allocation was performed by a statistician not involved in data collection.’. So, this is very unclear, and I suggest the authors rewrite this bullet point. Finally, if not able to provide a measure of body weight or body composition, this should be treated as a limitation of the study.

The sports and nutrition experts who were responsible for the intervention and collected the data for both intervention and control group could not be blinded as they only offered the intervention to patients of the intervention group while the control group continued to receive usual care.

The bullet point was changed to (p.4, l.8f):

- Sport and nutrition experts conducting the intervention and assessing the outcome in both groups could not be blinded due to the study design

The randomization process was done independently by a statistician not involved in any other parts of the study.

We added the descriptive statistics of BMI and muscle mass to the supplements. However, as this was not a study powered to conduct inferential statistics results cannot be interpreted as such and a main trial is warranted to prove the effectiveness.

Specific comments:

1) Abstract, Objectives, ‘[...] serious disease’ – severe or any other word may work better. All diseases are sort of ‘serious’.

We changed the wording to “a severe disease”

2) Introduction, page 4, lines 11-17 – Please, provide a reference.

References were added to the manuscript.

3) Introduction, page 4, lines 16-27 – The sentence is a bit confusing. Could the authors rephrase?

This paragraph has been rewritten based on your earlier suggestions. It now states (p.5, l. 4ff): “Major side effects of ovarian cancer and its treatment are cancer cachexia, sarcopenia, frailty, and malnutrition. All are leading to either loss of skeletal muscle mass and/or fat mass of the patient and are associated with decreased health-related quality of life (HRQoL), cancer related fatigue (CRF) and poorer outcome (3, 4). As these syndromes share similar etiological factors such as reduced food

intake, inflammation, hormonal changes, increased energy requirements and reduced physical activity (5) more than one can be present in the same patient at the same time. Hence, a combined intervention consisting of an exercise and nutrition program may be most successful to address these syndromes in patients with advanced cancer (6, 7).”

4) Introduction, page 4, lines 25-27 – “Exercise equivalent”?

The word equivalent was deleted

5) Introduction, page 4, lines 25-29 – “Cardiopulmonary fitness” is not so common. I suggest change to ‘cardiorespiratory fitness’.

We changed the wording based on your suggestion (p.5, l. 13)

6) Introduction, page 4, lines 28-34 – “[...] significantly improved HRQoL”. The study in question did not show improvements but a significant positive association between higher physical activity levels and quality of life. Please, amend the sentence.

The sentence (p.5, l.14f) was changed to: “Adherence to lifestyle recommendations such as physical activity and nutrition before diagnosis was associated with a significantly higher HRQoL (10).”

7) Introduction, page 4, lines 47-49 – “Yet, Randomized controlled trials...”. Randomised should be lower-case.

We corrected the typo

8) Introduction, page 4, lines 50-52 – “[...] bimodal intervention”. Better expand to ‘exercise and nutrition interventions’ rather than bimodal.

We changed the wording as suggested.

9) Introduction, page 5, lines 15-17 – “[...] in-person assessments” What do the authors mean by this? I would recommend rephrasing the sentence in question.

The feasibility outcomes did not require the patient to come to the clinic for an in-person assessment. However, as we were planning to move to a major trial after completion of the pilot study, we wanted to investigate whether patients would be willing to additionally take part in assessments that required personal visits at the clinic.

We changed the wording to: “Furthermore, assessments requiring visits to the hospital (in-person assessments) as planned for a main trial were conducted (e.g. HRQoL, CRF, muscular strength and quality, nutrition habits and quality) to investigate acceptance and safety in ovarian cancer patients.” (p.6, l. 6f)

10) Measures, page 7, lines 56-60 – Please, remove the first bracket of ‘(1)’ and ‘(2)’ since the references are in the same style.

We changed our whole manuscript accordingly.

11) Results, page 9, lines 13-17 – “The majority (73.3%) of patients was diagnosed as having advance stage disease”. Please, specify that this refers to stage III and IV patients.

This includes stages III and IV. We added this information to the text (p.10, l.15).

12) Table 1 and results section – Sports or sports interventions? What does that mean? Do the authors are referring to physical activity levels or exercise sessions? Please, clarify throughout the text.

In table 1 there is a footnote explaining that sports is assessed using the SQUASH questionnaire. We checked throughout the text, but did not mention the sports levels anywhere else. They were assessed, because for our main trial we will need to adjust for additional private engagement in any sports or physical activity. For this feasibility trial they have not been further analysed.

We changed the wording in our whole manuscript to “exercise intervention” to prevent any further confusion.

13) Results, page 11, lines 48-52 – Please, remove this first sentence. This was already informed in the methods section.

The sentence was changed to: “Adherence to the nutrition intervention in terms of caloric and protein intake showed that patients of the intervention group increased their protein intake from 65.8 gram (g) per day at baseline (T0) to 107.9g per day at T2.”

14) Results – Where is the nutritional information for the control group? This should also be informed.

On page 15 line 8-11 we compared the course of nutrition parameters in the IG and CG.

15) Results – Please, see my comment about statistical analysis above (point 9).

Answered under point 9

16) Discussion – Please, see my comment about the first paragraph of the discussion (point 1)

We changed our manuscript accordingly.

17) Discussion, page 16, lines 42-44 – “[...] rates of 70 – 100 stated a recent review” stated in a recent review.

We corrected the sentence in our manuscript.

18) Discussion, page 17, lines 3-4 – “by previous studies (10)” but is only one study.

The reference is a systematic review and reports on several studies regarding the subject, we added this information to the manuscript.

19) Discussion – Please, remember to adequate the discussion section accordingly to the results after informing statistical differences between groups.

We did not test for statistical differences between groups in our analyses, because this feasibility study was not powered to do so. Hence, we only reported and discussed the descriptive statistics.

Answers to Reviewer 2:

We would like to thank Dr. Cartmel for taking the time to comment on our manuscript. We found her feedback to be of great help and believe that the quality of our manuscript has increased due to her feedback.

Reviewer: 2

Dr. Brenda Cartmel, Yale University School of Public Health Comments to the Author:

The manuscript describes the results of a feasibility study of a 12-month exercise and nutrition intervention for ovarian cancer patients initiated during first-line chemotherapy.

Comments to the author:

a) Line 48: 'randomized' the 'r' should not be capitalized.

We corrected the typo.

b) Page 7, line 40: 'study coordination' I believe should read 'study coordinator'.

We changed the wording accordingly.

c) Page 7, line 42: Can the authors clarify, if the study coordinator conducted the baseline assessment and if so, when the study coordinator became aware of the group allocation for each patient? As currently written, it appears it was prior to the baseline assessment.

The study coordinator was not involved in the assessment at any time-point. However sports and nutrition experts who were responsible for the assessment could not be blinded due to the study design. This is a limitation that we have mentioned in the strength and limitation section. In our main trial assessment of all outcomes will be done by an independent expert who is fully blinded, which unfortunately was not possible for our pilot study.

d) Page 7, line 53: reference 16 is duplicated.

We corrected this mistake.

e) In some instances, the physical activity intervention is referred to as the 'exercise' intervention (e.g., page 8, line 25 and in some instances the 'sports program' (e.g., page 9, line 18). Suggest keeping the wording consistent, 'exercise' seems more appropriate than 'Sports' (i.e., a definition of sport: 'an activity involving physical exertion and skill in which an individual or team competes against another or others for entertainment').

We completely agree and have changed the wording to exercise intervention throughout the whole manuscript.

f) In the paper the home-based training is described as including endurance, resistance and balance exercises (page 8, line 30). A more comprehensive description of the training is needed and doesn't appear to be provided as stated in reference 23. For example, is the endurance exercise predominantly walking? What are the resistance exercises that are recommended? Is the goal to do each of endurance, resistance and balance exercises every day?

Also in response to comments of reviewer 1, we have added further information about the intervention on page 7, l. 12ff, and have included to the supplements the whole exercise catalogue, which was used as a basis to tailor an exercise program adapted to each patient.

g) Similarly greater detail regarding the nutritional intervention is needed for in phase 1 (page 8, lines 30-40). Was the goal to increase calorie intake in all patients? Was there a calorie goal based on initial weight, weight change during phase 1, initial calorie intake?

As most patients with ovarian cancer suffer from weight loss and malnutrition after surgery and during chemotherapy the general goal was to maintain or increase patients' calorie and protein intake. Recommendations were generally based on oncology guidelines that recommend a daily protein intake of 1.2-1.5kg/body weight in kg and can be increased to 2g/kg body weight if the patient is at high risk of malnutrition. However, as ovarian cancer patients are at much higher risk of malnutrition than other cancer patients there was no specific goal regarding calorie or protein intake and recommendations were highly individualized, based on individual needs, body weight and BIA parameters.

We added further information to the intervention on page 8 line 22ff

"Patients who were in need of an increased calorie and protein intake were advised to consume several smaller meals throughout the day. Nutritionists recommended the use of oils and butter if necessary. Furthermore, patients were educated about suitable types of foods and drinks that are high in protein, fat or energy. If deemed necessary oral sip feeding was suggested. These recommendations were based on the patients development in weight as well as other body composition parameters derived from BIA measurements (e.g. phase angle, muscle mass) Recommendations regarding calorie and protein intake were based on individual needs and adapted to patients weight development as well as body composition parameters assessed through BIA measurement."

h) Are any written/online instructions provided regarding the exercise and nutritional intervention page 8, line 25)?

We added the informational material that was handed out to the patients during nutrition counselling as well as the training catalogue including all exercises that were used to tailor each patients program to the supplements.

i) Can the authors quantify the reasons for refusal to participate in the study (page 9, line 46-48) and in the consort diagram? Is it possible to compare demographics and disease characteristics in those who were randomized to those who were eligible but chose not to participate in the study? This information would be helpful in knowing factors associated with participation e.g., are younger patients more likely to participate.

We agree that this would be helpful information. However, we do not have the patients consent to extract information from their clinical records.

j) Page 10, line 14; 'was' should be.

Page 10 line 4 is a table. I'm unsure which sentence you are referring to.

k) Page 12, lines 3-8; The authors stated that all 15 participants completed T0 and T1 in line 3. However, in line 8, it is stated that 13 patients completed the T1 assessment. Please reconcile.

We corrected the sentence it now says "13 patients completed the T2 assessment.

l) Page 12, line 59 'a patient of the of the intervention group'- 'of' should read 'in'. Please check this though out the manuscript.

We corrected this mistake throughout the manuscript.

m) Page 12, line 56: The calorie intake is reported in grams per day. This unit seems incorrect.

We corrected the measurement from g to kcal

n) Table 2: It is unclear what the data regarding the accelerometer refers to. Was the accelerometer used in the 6-minute walk test? Please clarify in the table, perhaps with a footnote. Similarly with the case report form. What data was collected via the case report form?

The accelerometer measured the amount of steps taken every day for seven days and was worn at home. The case report form included all questionnaires that were used in this study.

We added footnotes to table 2

o) Page 17, line 43; Missing '%' after 70-100.

We add the missing %

p) Page 18, line 50: 'lead' should be 'led'

We corrected the typo

q) 'Allocation concealment mechanism' – it is stated that this is describe in the published study protocol (Ref 23), but I am unable to find this information.

On page 7 under "procedure" we state the following: "Group allocation was performed by a statistician not involved in data collection. Information on group allocation was conveyed to the study coordinator responsible for making an appointment with the patients for the baseline assessment as well as the physiotherapist and nutritionist responsible for the intervention and outcome assessment in both groups.

VERSION 2 – REVIEW

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|-------------------------|---|
| REVIEWER | Lopez, Pedro Edith Cowan University School of Medical and Health Sciences |
| REVIEW RETURNED | 16-Dec-2021 |
| GENERAL COMMENTS | Thank you for your responses to my suggestions/comments. I do not have any further suggestions. |