PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Translation and Validation of the Cancer Related Fatigue Scale in Greek in a sample of patients with Advanced Prostate Cancer
AUTHORS	Charalambous, Andreas; Kaite, Charis; Constantinou, Marianna; Kouta, Christiana

VERSION 1 - REVIEW

REVIEWER	Professor Daniel Kelly School of Healthcare Sciences Cardiff University, UK. I work with Dr Charalambous on the board of the European Oncology Nursing Society.
REVIEW RETURNED	05-Apr-2016

GENERAL COMMENTS	Thank you for inviting me to review this paper. It is a useful addition to the literature on fatigue assessment in Greek prostate patients. There are some ares for improvement. First there is a detailed review section concerning tools early in the paper but a very short description of the methods for this particular study. I would suggest expanding the methods section to explain how, when and where recruitment took place as contextual information is important to the final conclusions. I cannot see confirmation of ethical approval. Overall was this study a replication of others carried out in other languages previously? If so this should be acknowledged. The paper could also be checked throughly for spelling and grammar as 'its' and 'it's' are used incorrectly in places. Some proof reading is also required for use full stops and the use one phrase 'The BFI.' on page 9. Whilst the paper does make a contribution I would have liked more information on advanced prostate cancer fatigue and why this work was needed for Greek speaking patients at this time (i.e. practice implications). This would help support the study and its conclusions, beyond the validation argument.

REVIEWER	Judith Manola Dana-Farber Cancer Institute Boston, MA, USA
REVIEW RETURNED	26-Apr-2016

GENERAL COMMENTS	The authors conducted a very useful validation of the Cancer Fatigue Scale in Greek. The work was well justified. Following are some suggestions for improvement. The background section provided an extensive review of various

	cancer fatigue instruments. Which ones have previously been validated in the Greek language? The background section should conclude with a summary statement and a statement of the rationale for doing the current study. The methods section should give the rationale for excluding patients with Karnofsky and AFI scores <50. The schedule for administering the questionnaires to the primary study participants should be provided. The method for obtaining informed consent from the patients and a description of IRB oversight for the study should be stated. It would also be useful to know why the comparison instruments were chosen. The analysis methods for test-retest reliability differed from those used in validating the original instrument. The use of the paired t-test for this is not clear. It is not valid to say that a non-significant p-value implies good stability; failure to reject the null hypothesis is not the same thing as accepting the alternative. The analysis methods section does not address the factor analysis; some of the terms in the factor analysis probably need to be explained for a general medical audience (e.g., KMO value, sphericity, eigenvalues). A table of patient characteristics would be helpful. A CONSORT diagram would also help to describe how many patients had repeat measurements. In the discussion, it would be helpful to have more comparison with the original validation. How did your results compare? Why might the mean scores be higher than in the original? I encourage you to find someone to help with the English language writing. This is nice work; it will be good to get it cleaned up for publication.

REVIEWER	Takeo Fujita Division of Esophageal Surgery National Cancer Center Hospital East
REVIEW RETURNED	12-Jul-2016

GENERAL COMMENTS	Authors evaluated the validity of "Cancer Related Fatigue" in Greek tanslated version of module. Although this study potentially have sevral limitation, the study was well organized in proper methods and results were reasonable.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name

Professor Daniel Kelly

Institution and Country

School of Healthcare Sciences

Cardiff University, UK.

Please state any competing interests or state ‘None declared’:
I work with Dr Charalambous on the board of the European Oncology Nursing Society.

Please leave your comments for the authors below
Thank you for inviting me to review this paper. It is a useful addition to the literature on fatigue assessment in Greek prostate patients. There are some areas for improvement.
1. First there is a detailed review section concerning tools early in the paper but a very short description of the methods for this particular study. I would suggest expanding the methods section to explain how, when and where recruitment took place as contextual information is important to the final conclusions.

Response: Additional contextual information was provided in terms of the methods section. Explicit information was provided on when, how and where recruitment tool place. (In methods section)

Response: The introduction of the paper was re-written (and re-organized in order to better introduce the reader to the problem of CRF and highlight the specificities of CRF in prostate cancer patients).

2. I cannot see confirmation of ethical approval.
Response: A paragraph has been now added in order to justify the confirmation of ethical approval (track changes text, under the methods section, page 6):

The study protocol was approved by the Cyprus National Bioethics Committee (CNBC 2010/06) Furthermore, an approval from the Research Committee of the Ministry of Health of Cyprus was obtained in order to gain access to Out-Patients Oncology Clinics of two public hospitals in Cyprus (MH 5.04.019). Prior to the study, the participants were given a written letter informing them of the aims and objectives of the study, and written consent was obtained by every participant. The study is in line with the principles described by the Helsinki Declaration. [54]

3. Overall was this study a replication of others carried out in other languages previously? If so this should be acknowledged.

Response: A line has been added (page 6), in order to acknowledge that the current study although has many similarities with the preceding validation studies is not following exactly the methods of the original study: “The current study regardless of its many similarities with preceding validation studies, is not following the exact methods of the original study [41] or the subsequent ones [51-53].”

4. The paper could also be checked thoroughly for spelling and grammar as 'its' and 'it's' are used incorrectly in places. Some proof reading is also required for use full stops and the use one phrase 'The BFI.' on page 9.

Response: Professional editing took place and appropriate corrections were made.

5. Whilst the paper does make a contribution I would have liked more information on advanced prostate cancer fatigue and why this work was needed for Greek speaking patients at this time (i.e. practice implications). This would help support the study and its conclusions, beyond the validation argument.

Response (This comment is addressed in conjunction with comment 2 by the second reviewer): On page 2 the following comments were added in the manuscript:

“Although prostate cancer patients tend to report lower severe fatigue levels compared to other patients (i.e. breast cancer patients) [7], they were most likely to report fatigue of more than 6 months’ duration [8]. Furthermore, patients with prostate cancer tend to report higher levels and more severe fatigue as the disease progressed [6]. This results in a considerable impact on a patient’s ability to function over time (physical and cognitive); hence, this symptom is among the most distressing of all those reported by patients. The prevalence of fatigue and the factors that predict inter-individual differences in trajectories of fatigue among prostate cancer patients can differ when compared to other types of cancer patients [9]. For example prostate cancer patients on androgen deprivation therapy (ADT), can experience ADT-induced fatigue. This fatigue is a complex multidimensional entity with multifactorial and complex pathophysiology that shares many overlapping features with other ADT-related toxicities such as depression, low mood and reduced libido [10].”

Furthermore, the aim of the study (page 5) was refined accordingly:

“Thus, the scope of the current study is a two-fold one. Firstly, is to translate and validate the multidimensional CFS in Greek and secondly to validate the scale in a specific group of patients, explicitly those diagnosed with prostate cancer. This is a major contribution to the relevant literature as the original study as well as the subsequent validations studies did not test the CFS in this specific population.”

Reviewer: 2

Reviewer Name

Judith Manola

Institution and Country

Dana-Farber Cancer Institute
Boston, MA, USA

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
The authors conducted a very useful validation of the Cancer Fatigue Scale in Greek. The work was well justified. Following are some suggestions for improvement.

1. The background section provided an extensive review of various cancer fatigue instruments. Which ones have previously been validated in the Greek language?

Response: A line clarifying the scales validated in Greek has been added accordingly to each scale (pages, 3-4).

The EORTC QLQ C30 has been validated in Greek.
The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), has been validated in Greek.[19]
The MDASI, has been validated in Greek.[21]
The BFI has been validated in Greek. [26]

2. The background section should conclude with a summary statement and a statement of the rationale for doing the current study.

Response: As per Reviewer's 1 comment number 5.

3. The methods section should give the rationale for excluding patients with Karnofsky and AFI scores <50. The schedule for administering the questionnaires to the primary study participants should be provided. The method for obtaining informed consent from the patients and a description of IRB oversight for the study should be stated. It would also be useful to know why the comparison instruments were chosen.

Response: It was explicitly described in the manuscript why these limitations were set for the participants. The following sentences were added accordingly: The Karnofsky Performance Scale index score was set at 50 to ensure that patients taking part in the study had not singnificant functional impairment that would not allow them to independently and accurately complete the assessment scale. The Attentional Function Index score was set at 50 to ensure that patients did not have severe cognitive alterations on their daily functioning, as these were imposed by cancer, treatment or fatigue.

Response: As per reviewer's 1 comment 2.

Response: in terms of why the EORTC C30 was chosen in this study the following sentences were added in the manuscript:
"The EORTC QLQ-C 30 was chosen primarily because it adopts a framework that is informed by the assessments of the physical and cognitive functions of the patient as well as the assessment of fatigue. This framework is similar to that of CRF, which characterizes fatigue in relation to physical, affective and cognitive elements [41]. Furthermore, its validity and sensitivity has been previously assessed in a population of advanced cancer patients [19]."

4. The analysis methods for test-retest reliability differed from those used in validating the original instrument. The use of the paired t-test for this is not clear. It is not valid to say that a non-significant p-value implies good stability; failure to reject the null hypothesis is not the same thing as accepting the alternative.

Response: As per the reviewer's suggestion the test-retest reliability was repeated with computing Pearson correlation coefficients. All the necessary changes/adjustments were made in the manuscript to accommodate these changes

6. The analysis methods section does not address the factor analysis; some of the terms in the factor analysis probably need to be explained for a general medical audience (e.g., KMO value, sphericity, eigenvalues).
Response: It was clarified in the manuscript (analysis section) that the "The construct validity of the survey was evaluated using a factor analysis with a Varimax rotation." (Page 8) Further details are given in page 10.

Furthermore, several paragraphs have been added explaining the terms used in the factors analysis: (pages, 11-12)

Kaiser-Mayer-Olkin is a Measure of Sampling Adequacy, both overall and for each variable. [56–58] In other words, it constitutes a summary of how small the partial correlations are, relative to the original (zero-order) correlations. KMO variables greater than 0.8 can be considered good (the component or factor analysis will be useful for these variables). It usually occurs when most of the zero-order correlations are positive. In addition, KMO values less than 0.5 occur when most of the

zero order correlations are negative. A value of .6 is a suggested minimum.

Bartlett's test of sphericity [59], tests the null hypothesis that the correlation matrix constitutes an identity matrix. An identity matrix in which all diagonal elements are 1 and all of diagonal elements are 0. In combination KMO and Bartlett's test of sphericity can provide a minimum standard which should be passed before a factor analysis should be conducted.

Eigenvalue: it's the variance in all the variables, which is accounted for by that factor. A factor's eigenvalue may be computed as the sum of its squared factor loadings for all the variables. [60]

6. A table of patient characteristics would be helpful.

Response: Table 1 describes the patient's characteristics and has been added (results section, page 8)

7. A CONSORT diagram would also help to describe how many patients had repeat measurements.

Response: Although a CONSORT diagram was not used as part of this manuscript it was clearly clarified how many patients were included in the test and the retest phases of this validation study. In page 8 (results section) the following sentence was added to clarify this:
"A total of 148 men, diagnosed with advanced prostate cancer completed the CFS (test), and 119 patient completed the assessment for a second time-retest (response rate 68.5% and 80% respectively)"

Furthermore, in the methods section the following sentence was added to clarify when the retest evaluation was conducted:

"The patients were recruited during the follow-up visit following the completion of the 3rd cycle of treatment where they completed the CFS. In order to assess the test–retest reliability of the scale a repeated measure was completed by the patients with an interval of 8 days."

8. In the discussion, it would be helpful to have more comparison with the original validation. How did your results compare? Why might the mean scores be higher than in the original?

Response: As per the reviewer's suggestion more comparison to the original study's findings was added in the manuscript's discussion section:

The following paragraph was added:

"The internal consistency of the CFS (total scale) was found to be high (0.916) and was higher than the original study (a=0.88). Furthermore, in both validation studies the cognitive subscale had the lowest alpha coefficients (0.79 and 0.79) and the physical subscale had the highest (0.92 and 0.89 respectively). In comparison with the original validation study [41], In addition, the three dimensions of the original fatigue scale appeared to also be present also in the Greek version of the scale, with a minor variation change. The good stability of the scale found in this study ($r=0.79$, $p<0.001$) was comparable to that of the original study ($r=0.80$, $p<0.001$). The mean scores in this study were found higher compared to the original across all the three subscales. This finding could possibly be attributed to the patients' advanced stage of the disease, in contrast to the original study where only 26.7% of the patients were classified as advanced prostate cancer patients. This is a finding consistent to the relevant literature [6]. Additionally, the patients in this study were on active chemotherapy treatment for their disease and this could have also contributed to experiencing more severe fatigue, an interpretation that is also supported by the literature [66]. No information is

provided in the original validation study on this aspect of the care. Despite the differences in the mean scores between the current and the original validation study, the findings showed that patients in both studies scored the lowest (indicating lower fatigue levels) in relation to the cognitive elements of fatigue. The current validation study also provided evidence on the criterion validity of the CFS, which the original and subsequent validation studies did not provide."

9. I encourage you to find someone to help with the English language writing. This is nice work; it will be good to get it cleaned up for publication.

Response: Professional editing took place in line with Reviewer's 1 comments.

Reviewer: 3
Reviewer Name

Takeo Fujita

Institution and Country

Division of Esophageal Surgery
National Cancer Center Hospital East

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
Authors evaluated the validity of "Cancer Related Fatigue" in Greek tanslated version of module. Although this study potentially have several limitation, the study was well organized in proper methods and results were reasonable.

Response: No further actions were taken, as per reviewer's comments.

VERSION 2 – REVIEW

REVIEWER	Judith Manola Dana-Farber Cancer Institute
REVIEW RETURNED	01-Sep-2016

GENERAL COMMENTS	This is a much improved draft of the manuscript. A couple of additional improvements are suggested. One more review of the English grammar and punctuation, especially in the methods and results sections, would be beneficial. The last lines of Table 4 showing the eigenvalues and % variance explained need some formatting - they are hard to read. Some aspects of the CONSORT checklist are not provided and would be useful (e.g., dates of enrollment).

VERSION 2 – AUTHOR RESPONSE

One more review of the English grammar and punctuation, especially in the methods and results sections, would be beneficial. The last lines of Table 4 showing eigenvalues and % variance explain need some formatting – they are hard to read. Some aspects of the CONSORT checklist are not

provided and would be useful (e.g. dates of enrollment).

Response

1. The manuscript has been checked for grammar and punctuation throughout. Emphasis was given in the methods and results sections as per the reviewer's suggestion.
2. Table 4 has been formatted so that all borders of the table are visible and values throughout can be easily read.
3. A CONSORT checklist or CONSORT flow diagram were not submitted in the original submission as this was not a Randomized Controlled Trial.