

REPLIES TO REVIEWERS

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: BCS: explain the acronym Table 1: very confused. Why authors present the total results? The p value is referred to the 2 groups, but when authors included the total, p value results became too confused. Among which groups, p values are referred to.... Table 2: authors should include the exact pvalue Table 3: also too confused. Why there are different study groups. Authors should make more readable this table

BCS (breast conserving surgery) was explained at first use in Methods.

Table 1: The column with total numbers has been eliminated. It is now more understandable that the p-values reported in the corresponding column refer to the comparison of the two study groups.

Table 2: exact p-values have been reported ($p < 0.001$ is the value reported by the statistics software during data analysis)

Table 3: This table report the Multivariate logistic regression for factors associated with the need of additional medical visits before chemotherapy in patients the ESAS Group (ESAS score > 3). The content of the table was explained in Results as follows:

“Based on multivariate analysis, women of the ESAS Group were more likely to undergo additional visits before chemotherapy for an ESAS score > 3 if they were aged > 60 years, received a mastectomy, or had tumour stage II/III (Table 3). We did not find any association between additional visits and immunohistochemical tumour classification or lymph node status. Age > 60 years was the strongest predictor of receiving additional medical visits before chemotherapy (OR 4.93, 95% confidence interval 1.26–19.25)”.

The table reports the usual values of multivariate analyses (Odds Ratio, St. Error, z-Score, 95% CI, p-value). However, to improve the readability of the table, the following modifications have been made:

- The p-value column was moved as last column in the left.
- An asterisk (*) indicates statistical significance.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Review Manuscript No. 75447 The Edmonton Symptom Assessment Scale (ESAS) as a useful tool for symptom assessment in

patients with breast cancer undergoing adjuvant chemotherapy. In a pandemic, a study that justifies the possibility of safely reducing the number of visits to the doctor by the breast cancer patients during courses of adjuvant chemotherapy (AC) is of undoubted interest. It is important that this study also touches on important economic, social and medical aspects.

We are grateful to our reviewer for pointing out the interest and strength of our work.

However, the presented manuscript, in my opinion, contains a number of serious shortcomings, mainly of a methodological nature. I. Title of the manuscript should reflect the purpose of the study.

The title has been changed as follows:

'The Edmonton Symptom Assessment Scale (ESAS) may safely reduce the number of medical visits in patients candidates for adjuvant chemotherapy for early breast cancer.'

II. ABSTRACT 1. Comparison of groups with and without ESAS is hardly worth including in the ABSTRACT, it can be limited to stating that the groups did not differ in variables.

In the abstract, we have simplified the first sentence in Results as follows:

'The study variables did not statistically differ between patients of the ESAS Group and no-ESAS Group regarding age, cancer stage, histology, tumour size, lymph node status, immunohistochemical classification, and type of surgery.'

2. By itself, the ESAS score does not reduce the number of patient visits to the doctor for breast cancer, but allows you to select a group of patients for whom it is safe to reduce their number.

We agree with this concept. The first sentence in Abstract conclusions was modified as follows:

'Our results suggest that the ESAS score may be used for selecting a group of breast cancer patients for whom it is safe to reduce the number of medical visits in the setting of adjuvant chemotherapy.'

3. Stages II/III of breast cancer are not early!!!.

This is an interesting comment. Technically, the definition of 'early BC' is when cancer is found only in the breast or nearby lymph nodes, and has not spread to other parts of the body, thus including Stage II and III. However, since most of the authors commonly use the term 'early BC' for Stages I and II, we have decided to remove the word 'early', as it does not alter the sense of the content of the manuscript.

4. It should be noted in abstract what kind of benefits (financial, reduced risk of covid infection, etc.) gives an assessment on the ESAS scale in oncological practice.

We agree with our reviewer. The last sentence in conclusions was modified to:

'Our results suggest that the ESAS score may be used for selecting a group of breast cancer patients for whom it is safe to reduce the number of medical visits in the setting of adjuvant chemotherapy. This may translate into several advantages, such

as a more rational utilization of human resources and a possible reduction of COVID-19 infection risk in oncologic patients.'

III. Introduction. The question of a safe reduction in visits can only be raised on the basis of prospective studies.

We thank our reviewer for pointing out this. Actually, since a prospective study involves a cohort of subjects and watching them for outcomes over a period, our study design is a prospective study. Thus, we have replaced 'retrospective' with 'prospective' matched pair study.

IV. Methods It should be clarified which groups of patients and at what time were included in the study (from January 2018 to November 2021; from January 2016 to August 2019; from January 2020 to December 2021). This information should be clarified and presented in a more understandable form.

Thank you for the suggestion. We have eliminated in methods '~~For the purpose of this study, we asked our database for patients who had undergone AC for Stages I-III breast cancer from January 2018 to November 2021.~~'

In 'Study design', we have now stated that 'In a case-matched analysis, data from 100 patients taking the ESAS (the ESAS Group) in the period January 2020 to November 2021 were compared with data of 100 patients who underwent AC according to the traditional modality, without the ESAS (the no-ESAS Group) during the previous period (January 2016-December 2019).

Please note that the time frame for each group has also be specified in Figure 1.

This also applies to Figure 1, which contradicts the manuscript text.

Please note that the time frame for each group has also been correctly specified in Figure 1 and now text and Figure 1 are consistent.

Page 4, line 5 "...percentage of patients requiring unplanned medical visits" - this indicator cannot be retrieved from the patient database, it is calculated. Rephrase.

Page 4, line 8-9 - "In the ESAS Group, also the percentage of patients requiring an additional medical visit before chemotherapy on the basis of an ESAS score > 3, was evaluated.". Probably also incorrect wording. Perhaps you meant that based on the ESAS score > 3, you identified patients who needed additional visits to the doctor and then calculated their percentage. Explain this point.

This is a correct observation. We have rephrased as follows: 'In the ESAS Group, patients who needed additional medical visits based on the ESAS score > 3, were identified. In both study groups (ESAS and no-ESAS) percentage of patients requiring unplanned medical visits (defined as visits for problems related to the surgical procedure or chemotherapy-related side effects), the number of unplanned medical visits, and grade 3-4 adverse effects during chemotherapy treatment, were calculated.'

...

V. Results. Page 6 "Six patients of the ESAS Group and 12 of the no-ESAS Group needed one or more unplanned visit during the AC duration, for a total of 8 and 18 visits, respectively (p = 0.057)." It's not clear. Were there 8 additional visits for 6 patients (1.3 per patient) and 18 for 12 patients (1.5 per patient)? But then the given

level of significance does not correspond to reality ($p = 0.057$). Or did you compare other indicators?

We agree that this finding needed to be better clarified. Moreover, we have recalculated the chi-square test and obtained a p -value = 0.035. We have modified to:

"There were there 8 additional unplanned visits for 6 patients in the ESAS Group, and 18 additional visits for 12 patients in the no-ESAS Group ($p = 0.35$)" The p -value was also corrected in the abstract and Table 2.

Page 6 "Forty-eight patients of the ESAS Group received an additional visit due to an ESAS score > 3 ." - It is unclear whether all patients with ESAS score > 3 were scheduled additional visits or not? This should be specified.

An ESAS score > 3 was a precise indication for an additional medical visit. We have better specified this in Study design: '...Therefore, each patient of the ESAS Group was scheduled to receive a total of three medical visits for the entire AC duration; an additional medical visit before each chemotherapy session was carried out according to the ESAS score (specifically in the **all** cases where the ESAS score was > 3).'

The authors should also present the distribution of patients by ESAS score, preferably in both groups.

According to the study design, the ESAS score was calculated only in patients of the ESAS Group (by definition, the control group was the no-ESAS Group). We have reported in Results and Table 2 that 48 patients of the ESAS Group required an adjunctive medical visit on the bases of ESAS score > 3 .

In general, study design raises questions: 1. it was a prospective study in which they planned 3 visits to the doctor for patients receiving AC and scheduled additional visits only for patients with an ESAS score > 3 , after which they compared the results with the standard scheme of patient visits to the doctor (16 visits per patient) during chemotherapy courses 2016-2019; 2. both groups of patients were recruited in 2020 - 2021 (one group was scheduled for 3 visits, and the second - 16), as follows from Figure 1; 3. or something else?

It is a prospective study where 100 BC patients receiving ESAS before AC in the period 2020-2021 were matched with 100 patients who did not receive ESAS before AC (control group from the period 2016-2019). Figure 1 was corrected to clarify the study design.

VI. Discussion. Page 7. Incorrect wording: "In the series described herein, we found that the patients who completed the ESAS questionnaire significantly received fewer medical visits during the chemotherapy period compared with patients of the control group." - Reducing visits to the doctor is not a consequence of completing the ESAS questionnaire. The patients originally had 3 visits scheduled! The use of a questionnaire allowed the authors to identify patients who required additional visits. As a result, you proved that the reduction in the number of scheduled visits, taking into account the ESAS score, did not affect unscheduled visits to the doctor and the number of complications of chemotherapy. This is the most important and interesting.

We are grateful for this suggestion aiming to improve the understandability of the main message of our work. Actually, the sentence as it is may sound equivocal. We have rephrased in this way:

'In the series described herein, we found that the use of the ESAS questionnaire allowed to identify patients who required additional medical visits before a chemotherapy cycle. To note, the reduction in the number of scheduled visits based on the ESAS score, did not affect the occurrence of complications from chemotherapy, and was associated to a reduced number of unplanned medical visits.'

Page 7. "Of note, the unplanned medical visits – that is, the outpatient visits for monitoring the disease and providing supportive care – were performed less often in the ESAS Group." - a somewhat controversial conclusion (1.3 and 1.5 additional visits per patient in the ESAS group and without ESAS.) In the discussion, I think it should not be argued that it is ESAS that reduces the number of visits, side effects of chemotherapy, etc. This is more likely due to the fact that ESAS accounting, on the one hand, identifies a large group of patients who do not need to visit a doctor during each course of chemotherapy, and, on the other hand, allows you to identify a group of patients with a high risk of complications and adjust the treatment, thereby reducing these risks. Moreover, you do not indicate whether the treatment tactics changed depending on the ESAS.

The sentence mentioned by the reviewer was eliminated, since it does not add to the message of the paper. We have looked at rate of complications from chemo as surrogate of safety of reduction of medical visits based on the ESAS score. We have added the following sentence in conclusions: 'Moreover, it implies that ESAS may help to identify patients who do not need to visit a doctor during each course of chemotherapy, as well as to identify a group of patients with a high risk of complications in whom a treatment adjustment is needed.'

The aim of the study was to investigate whether the ESAS can be used to safely reduce the number of medical visits in women with breast cancer undergoing adjuvant chemotherapy. Change of treatment was not among the endpoints of the study, but this issue is under consideration for an ongoing work regarding a new cohort of patients.

Table 2. "No" - not used to indicate quantity. Use "number" or "n" Thus, the authors should more precisely define the type of study (prospective or retrospective) and its design, change the title in accordance with the purpose of the study, and present the results more correctly, in accordance with the comments.

In Tables and Figure 1, "No" to indicate number was substituted with "N". We have defined the study as prospective. Title was changed and results presented according to reviewer's suggestions.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: 1. The manuscript focus on The Edmonton Symptom Assessment Scale (ESAS) as a useful tool for symptom assessment in patients with breast cancer undergoing adjuvant chemotherapy, after checked the references in Pubmed, there are so many related articles.

We agree with our reviewer, there are many articles about the use of the ESAS score in metastatic breast cancer and relative references were included in our paper. However, few studies have looked at the usefulness of the ESAS score in the setting of adjuvant chemotherapy (chemo administered after radical surgery in patients with no distant metastases) for breast cancer.

2. Tables should use three line tables ? following the journal requirements.

Tables lines were modified according to review guidelines of BPG articles.

3. Figures not clear need dpi 300 more.

Figure 1 has been submitted as a PowerPoint file, and the tables as a merged Word file, as requested.

4. English need more polish.

Since some changes have been made in the manuscript according to reviewers' comments, we have sent the article for a new proofreading. A new certificate from Proof-Reading-Service has been uploaded with the re-submission.

Reviewer #4:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This is a good clinical research which used the ESAS system to reduce the medical visit of breast cancer patients undergoing AC. Medical visits in the pre-chemotherapy assessment represent a significant burden on the oncological care system, this research could supply a good choice to resolve this problem. The design is good and discussion part is also justified.

We thank our reviewer for highlighting the interest of our paper.