Original article

The course of cancer related fatigue up to ten years in early breast cancer patients: What impact in clinical practice?

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ABSTRACT

Little is known about the cancer related fatigue (CRF) along cancer course and risk factors that could predict CRF development and persistence in breast cancer (BC) survivors.

This prospective study detected incidence, timing of onset, duration of CRF, impact on QoL and psychological distress.

Seventy-eight early BC patients, undergoing chemotherapy (CT) followed or not by hormonal therapy were assessed for QoL and psychological distress by EORTC QLQC30 and HADs questionnaires. Fatigue was investigated with mix methods, structured interview and psychometric measures. A qualitative analysis was added to assess the behavioral pattern of CRF.

Low fatigue levels were identified after surgery (9%), increasing during (49%) and at the end of CT (47%), maintaining after 1 year (31%) and declining up to ten years of follow-up. Prevalence of CRF was higher at the end of CT and lower at follow-up. At the end and after 1 and 2 years from CT, persistence of CRF was associated to anxiety in 20%, 11% and 5% and to depression in 15%, 10% and 5% respectively. A relationship between CRF and psychological distress was observed; patients presenting depression and anxiety before CT were at higher risk for fatigue onset at a later period. A relationship between fatigue and QoL was noted at the end of CT.

Our study shows the fatigue timely trend in early BC patients from surgery, CT and follow-up. Identification of biological, psychological, social predictor factors related to fatigue could be helpful for early interventions in patients at higher risk of developing fatigue.

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1. Introduction

The increasing effectiveness of adjuvant therapies has resulted in an ever-increasing number of cancer survivors. However, many survivors experience long-term adverse effects due to previous treatments which deteriorate health-related quality of life (HRQOL) [1–3].

One of the most frequent adverse effects reported in cancer patients undergoing systemic treatments is fatigue.

Fatigue is a condition that involves a subjective sense of weakness, lack of energy and/or tiredness. The etiology of cancer-related fatigue (CRF) has not yet been thoroughly elucidated, although it may involve several physiological, biochemical, and psychological systems which in turn might vary according to kind of tumor, stage of disease, and treatment [4].

In the analysis carried out on BC patients undergoing treatment and in the first 5 years after completing treatment, it was shown that depression was one of the strongest factors related to CRF [5–7]. Despite the recent rise in research interest in this area, the nature and direction explaining these variables remain uncertain. Other studies suggest that CRF and depression are independent conditions in cancer patients with differing patterns over the course of disease and with different underlying mechanisms [8,9]. These conflicting results could also be related to the measurements utilized and to their ability in distinguishing CRF from depression [10–13]. There is a need for validated instruments able to accurately assess CRF and distinguish CRF from depression. A clear

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understanding of the mechanisms underlying the relationship between CRF and depression may define a better prevention and care strategy.

In addition, anxiety is consistently associated with CRF despite that this psychological variable has not been extensively explored [2,14].

Other aspects include the relationship between CRF, disease, treatment-related factors, socio-demographic variables, age at early BC diagnosis and pre-treatment CRF score. Conflicting factors were reported in this field [1,5,15—23].

The CRF is one of the most notable symptoms associated with cancer and its treatments. It is reported to be the single most distressing symptom with the greatest negative impact on HRQoL [1—3,24—25]. Lower HRQoL and its negative effects on daily functioning have been reported in patients undergoing chemotherapy as well as in some BC survivors after chemotherapy [26,27].

CRF may lead to poor compliance with chemotherapy (CT) regimens [28,29] and is often the reason for patients discontinuing the treatment [30].

There is not much data regarding the long-term trajectory of CRF or the relationship with HRQoL and psychological distress.

Previous findings reported that CRF is typically resolved in the year after completing treatment but, to date, approximately 30% of patients experience more persistent CRF that may endure for up to 10 years or more [22]. When CRF persists for 6 months or longer it is chronic fatigue (CF), which is of special relevance in cancer survivors [21,31] but to date not yet prospectively studied.

Previous studies on BC patients treated with systemic therapies showed rates of CRF ranging between 35% and 40% at 2 and 3 years after therapy, respectively compared with 11% in those without a history of cancer [32,33]. The latest findings have reported a CRF incidence rate of about 10%—24% before adjuvant CT and 26%—31% at the end of these treatments [17,34]. Reports from prospective studies after adjuvant therapies span from a prevalence of 39% and 23% at 2 and 4 years, respectively [7], to 34% and 21% at 3.5 and 6.5 years, respectively [22]. Up to now there has been no recent prospective results that have verified the permanence of CRF after 5 years from diagnosis of early BC with drugs used in the adjuvant setting, both as chemotherapy and aromatase inhibitors or tamoxifen. So, it is very important to study the fatigue phenomena in the course of 10 years after systemic treatment especially in light of the increase of survival of women affected by breast cancer and the impact that CRF could have on quality of life.

Here, we report findings of a mono-institutional prospective study on CRF in patients with diagnosed BC and treated with CT followed or not by hormonal therapy (HT).

In this study we carefully explored the time course and the behavior over 10 years of CRF and psychological distress; the time course of HRQoL and the relationship between CRF and HRQol, psychological distress and clinical features in early BC patients undergoing CT ± HT.

The CRF will be investigate with mix methods, structured interview and psychometric measures.

2. Material and methods

Patients with newly diagnosed early BC and who were eligible for adjuvant CT followed or not by HT were included and assessed after surgery for primary tumors. The patients were followed prospectively and were participated in a long-term follow-up study.

Exclusion criteria included patients with ipsilateral breast and/ or axillary recurrences and/or a previous contralateral BC. Moreover, patients with psychiatric illness, unable to fill in questionnaires, with concurrent chronic/life threatening disease where fatigue was a prominent symptom were not eligible.

The study was approved by the Ethics Committee of Regina Elena National Cancer Institute in Rome (Italy). Informed consent was signed by the patients at study entry.

Assessment. Patients were assessed by an oncologist throughout the period of treatment and by a psychologist once week before starting CT, after 3 or 4 cycles and 1 month after 6 or 8 cycles of CT; after the end of CT all patients were assessed by an oncologist and a psychologist at 6, 12 months and then annually for the following 10 years from the start of CT. The follow up by oncologist was carried out in accordance with the international guidelines (American Society of Clinical Oncology).

For the results, we defined the assessment of patients in relation to the time of CT and to the follow up in which patients were submitted or not to HT (from the end of CT to a total of 5 years): T0 (one week before the start of CT), T1 (after 3 or 4 cycles of CT), T2 (at the end of CT and at the start of HT for those patients with positive hormonal receptors) T3 (after 1 year to the end of CT, and with or without HT), T4 (after 2 years to CT), T5 (after 5 years to CT), T6 (after 10 years to CT).

Adjuvant treatments. Adjuvant CT included regimens with three weekly anthracyclines followed or not by taxanes or not including anthracycline regimens (such as Cyclophosphamide, Methotrexate, Fluorouracil [CMF]). Adjuvant HT consisted of tamoxifen or aromatase inhibitors in premenopausal or in postmenopausal patients, respectively. After CT patients underwent complementary radiotherapy in case of conservative surgery and/or metastases in axillary lymphonodes ($\geq$4).

Toxicity assessment. Toxicity was assessed before each drug administration, via physical examination, hematology and biochemistry exams. Adverse events were graded in accordance with the National Cancer Institute (NCI) common toxicity criteria (NCICT-CAE) version 4.0 [35].

CRF and Psychological measurement. In order to perform psychological assessment, a battery of questionnaires aimed to assess the quality of life (EORTC QLQ C30 and QLQ BR23 for BC module), psychological distress (HADs) and CRF (FACT-F) were administered.

The EORTC QLQ-C30 questionnaire (version 0.3) explores the following functional areas: physical, role, emotional, cognitive, and social as well as global quality of life index. It also includes a number of multi-item scales and single items that assess a range of physical symptoms (CRF, nausea and vomiting, pain, dyspnea, sleep disturbance, loss of appetite, constipation, and diarrhoea) as well as financial difficulties [36].

The EORTC scores range from 0 to 100. Higher scores represent a better level of QoL in the functional areas, but a higher degree of symptoms [37].

The course of distress was investigated with the HAD scale which is a reliable and valid instrument for assessing anxiety and depression in patients. Hospital Anxiety and Depression scale (HADS) [38] is a 14 item questionnaire consisting of two subscales, anxiety and depression. Each item is rated on a four point scale from 0 to 3 giving a maximum score of 21 on each subscale. According to Carroll et al. [39] scores from 0 to 7 indicate normal levels, scores between 8 and 10 on Anxiety and Depression subscales indicate borderline cases, while scores => 11 identify clinical cases. The cut-off scores of 14 and 19 on the HAD-S Total were used to evaluate likely psychiatric caseness and caseness. respectively. The advantage of using the HADS is that its depression subscale does not include any physical symptoms such as lack of energy or sleep disturbance, thereby reducing potential contamination of the relationship with a measure of CRF. In this study, psychological distress has been assessed with a mean score and severity threshold.

In addition the persistence of psychological distress was assessed on the basis of the number of patients showing levels $\geq$8

of psychological distress continuously from 0 up to ten years of follow-up (T6).

The FACT-F and -Anemia scales, in particular, have shown strong associations with hemoglobin level, functional status, and global QOL [40—44].

The Functional Assessment of Cancer Therapy-Fatigue (FACT-F) subscale is a 13-item questionnaire that is part of the 20-item anemia module (FACT-An) of the FACIT quality of life assessment system. The FACT-F has well-validated psychometric properties [40] and has been used in a large number of intervention studies to treat CRF [45]. Scores can range between 0 and 52 with lower scores indicating greater CRF [46]. For this study, italian validated version of FACT-F was used.

Some authors detected a cut-off of 36 as the optimal score to identify patients with and without significant CRF [15]. The persistence of CRF was assessed based on the number of patients who showed levels of fatigue <36 continuously from T1, time of CRF onset, and up to ten years of follow-up (T6). The association between CRF and psychological distress persistence was also evaluated.

To the evaluation which utilizes the cut-off of 36, a qualitative analysis was added to assess the change in CRF patterns according to the clinically significant difference (SCIDs) in changes over time within every single patient. Cella has identified the deviation of three points in the FACT questionnaire as equivalent of a clinically significant change in CRF [40]. According to SCIDs, the direction of change has been classified in "improvement", "worsening" and "stable" classes: "improvement" involves an increase in CRF scores of at least three points, "worsening" a decrease of at least three points, "stable" a decrease or an increase of less than three points.

Formal tests, such as the EORTC QLQ, may fail to adequately capture the CRF patient experience. For this reason, the study has utilized a structured interview carried out for a QoL assessment project in different early cancers. The interview evaluated the patient perception of treatments sequelae that most impacted his quality of life. The patient perception of these sequelae, some common to all disease sites, and others unique, is not included in the questionnaires but essential in the lives of patients.

For this study, we analyzed only two areas of the structured interview that were more specific to fatigue in BC: the patient's perception of CRF as the experience which has the most impact on daily functioning, during treatment and follow-up; CRF onset and decline compared to CT infusion time.

A comparison was made between the CRF patient's subjective perception, taken from the interview and the CRF scores stemming from the FACT-F.

2.1. Statistical analysis

Data on the psychological assessment were summarized using mean and standard deviations or absolute counts and percentages. Differences between mean values were evaluated with the Student's t-test, paired or not according to the setting. Associations between patient characteristics and data dichotomized according to cut-off values were analyzed with the chi-square test. Repeated measurements analysis of variance (ANOVA) was used to test differences in CRF over time. A multiple correspondence analysis (MCA) was applied to investigate the interrelationships among the factors considered. This kind of analysis is mainly descriptive and resumes information on association among factors considered through a graphical representation. IBM SPSS version. 21 was used as statistical software.

3. Results

From September 2002 to January 2004, a total of 112 patients

were identified. Patient characteristics are summarized in Table 1. Included and evaluate patients are shown in Fig. 1. Thirty-four patients did not meet the inclusion criteria, therefore a total of 78 patients were evaluable for the study. At T2 and T3, the number of patients who continued the study were 75 (3 patients continued treatment in other centers) and 71 (4 patients refused to continue due to too much study burden), respectively. At T4, 65 patients (6 patients refused due to personal problems, medical issues or too much study burden), and 62 patients at T5 (2 deaths from disease, 1 patient refused to continue the study), and 56 patients at T6 (3 patients had progression disease and 3 lost to follow up).

No differences were observed both in terms of age and menopausal status between patients with prolonged follow-up compared with patients lost to follow up (56 vs 22). In contrast a statistically significant difference was shown in patients underwent to OT (p = 0.01).

All patients were examined for toxicity. The most common severe toxicities (grade 3 and 4) were leukopenia and neutropenia reported in 24 (30.7%) and 17 (21.7%) patients, respectively, and 4 (5.1%) patients were affected by neutropenic fever. Severe thrombocytopenia was not observed. From the start of treatment, 24 (30.7%) patients were observed to have reduced levels of hemoglobin of 2 gr/dl (median value of Hgb 14.2 vs 11.8). Severe non hematological toxicities were uncommon. Alopecia was reported in the majority of patients (89.7%), moderate nausea and vomiting were observed in 20 (25.6%) and 17 (21.7%) patients, respectively. Mild peripheral neurotoxicity was observed in 28 (35.8%) patients.

3.1. CRF roller coaster effect

The analysis of the onset and decline of CRF during treatment

Table 1
Patient's characsteristics.[a]

	N° (%)
Total patients enrolled	112
Patients evaluable for the study	78 (69.6)
Age (years) (median and range)	49 (26—74)
Menopausal Status	
Pre	41 (52.5)
Post	37 (47.5)
Hormonal Receptor	
Positive	43 (55)
Negative	35 (45)
Type of Surgery	
Quadrantectomy	54 (69)
Mastectomy	24 (31)
Stage of disease	
I	39 (49)
II	26 (34)
III	13 (17)
Adjuvant Chemotherapy plus Hormonal Therapy	43 (55)
Adjuvant Chemotherapy alone	35 (45)
Chemotherapy	
Anthracycline alone	25 (32)
Anthracycline/Taxanes	39 (50)
Not including anthracycline/taxanes	14 (18)
Hormonal Therapy	
Tamoxifen[b]	26 (33)
Aromatase Inhibitor	17 (22)
Radiotherapy on the breast ± axilla	65 (58)
Basal value of haemoglobin (gr/dl) (median and range)	12 (8.5—15.2)
Global QoL (mean ± standard deviation)	72.31 ± 13.26
Anxiety (mean ± standard deviation)	7.99 ± 2.47
Depression (mean ± standard deviation)	7.81 ± 2.81
CRF (mean ± standard deviation)	45.13 ± 6.14

[a] Among 112 patients enrolled in the study, 34 of them did not meet the inclusion criteria.
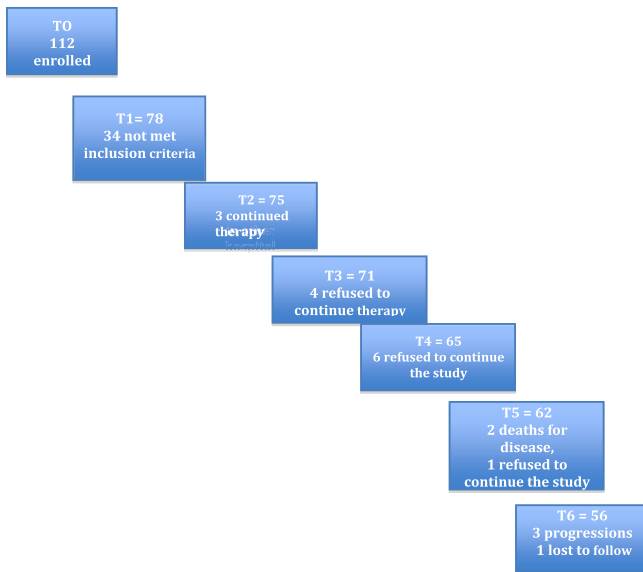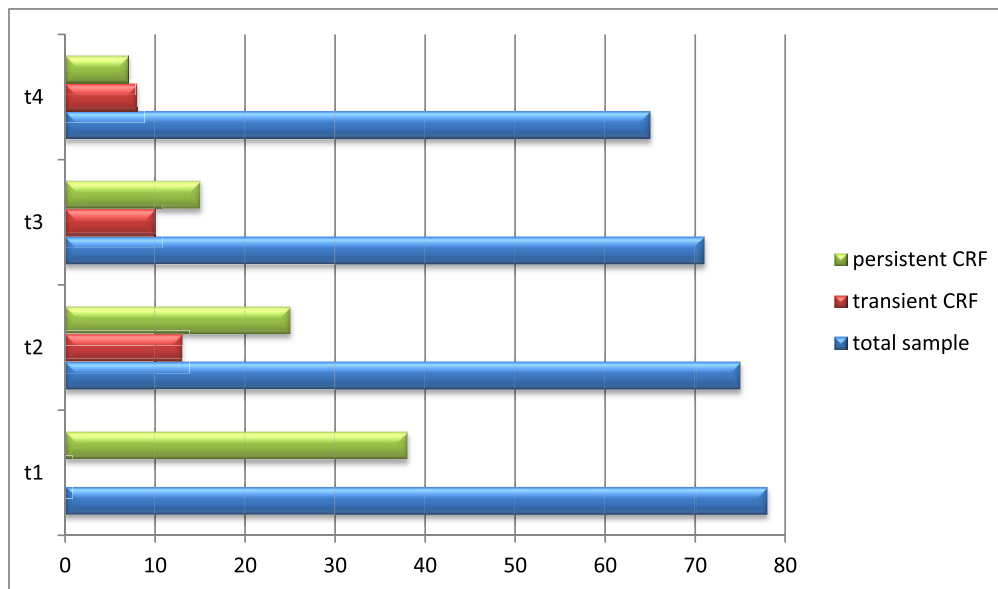[b] Tamoxifen ± LHRH analogue.

Fig. 1. Flow chart of included and evaluated patients on different study time.

showed a peak between 3 and 5 days after administering the drug and normalization took place within 7 days prior to the next cycle in 81% of patients.

3.2. The time course of CRF

Fig. 2 Time course of CRF according to the cut-off value of 36.

CRF was detected at baseline in 7/78 (9%) patients, in 38/78 at T1 (49%), in 35/75 at T2 (47%), in 22/71 at T3 (31%), in 8/65 at T4 (12%), in 2/62 at T5 (3%) and in 3/56 at T6 (5%).

3.3. CRF persistence

Compared to a total of 38 (49%) fatigued patients at T1, the persistent CRF regarded 25 patients (33%), 15 (21%) and 7 (11%) patients at T2, T3, T4, respectively (Fig. 3). At T5 and T6 no patient showed persistent CRF (Fig. 2).

3.4. Qualitative analysis among patients with CRF

Out of 38 fatigued patients at T1, 11 (29%) showed an improvement with CRF levels above the cut-off rate of 36 (no CRF: 29%), 5 patients improved in terms of SCIDs but continued to have CRF <36 (13%), 7 patients further worsened (18%) and 13 patients (34%) showed levels of fatigue steadily below threshold at T2. For 2 patients (5%) data are missing.

At T2 CRF rose in 10 patients consequently the number of patients with fatigue increased to 35 (47%).

At T3 6 (8.4%) patients showed an improvement with CRF levels above the cut-off of 36 (no CRF 60%), 1 out of ten patients (10%) worsened further, and 3(30%) showed levels of fatigue steadily below threshold.

At T3, the CRF increased in 3 patients, bringing the number of patients with CRF to 22 (31%). In all three patients the CRF discontinues to T4.

At T4, 15 patients showed an improvement with CRF levels above the cut-off (no CRF 68%), 2 patients (9%) improved but continued to have CRF < 36, 1(4%) worsened further, while 4

In Y axis is represented the evaluation times: T1 (after 3 or 4 cycles of CT), T2 (at the end of CT and at the start of HT for those patients with positive hormonal receptors) T3 (after 1 year to the end of CT, and with or without HT), T4 (after 2 years to CT). In X axis is represented the total sample of 78 patients, the subgroup of patients with persistent CRF and transient CRF.

Fig. 2. CRF persistence.

patients (19%) showed levels of fatigue steadily below threshold.

3.5. Comparison between the subjective perception and the FACT-F scores

According to the CRF patient's subjective perception, at T1 45 (58%) patients referred that CRF was the worst condition impacting daily functioning, and only 28 (62%) of them had a CRF <36; at T2 32 (43%)but only 23 of these (72%) have CRF < 36. At T3 10 (14%) patients referred that the CRF is the worst condition, but only 8 (80%) have scores below 36.

3.6. The course of psychological distress

3.6.1. Anxiety

The anxiety mean scores, assessed with HADs, showed a stable trend up to 24 months after CT (T4) with a mean score of 8.01, and an improvement in the subsequent times with a mean score of 6.7.

The anxiety assessed according to the severity thresholds showed that at T0 the percentage of patients with reactive and pathological anxiety is greater than that of patients with normal scores (60% vs. 40), which further increased at T1 (64% vs. 36%), returned permanently to baseline levels from T2 to T4, and decreased steadily in the follow-up at 5 and 10 years (Table 2).

3.6.2. Depression

The depression mean scores, assessed with HADs, showed a stable trend until the end of CT (T2) with a mean score of 8.1 and an improvement to 10 years of follow-up with a mean score of 6.8.

Depression was assessed according to the severity thresholds and showed that at T0 the percentage of patients with normal depression is comparable to that of patients with reactive and pathological depression (47% vs. 53%). At T1, the number of patients with reactive and pathological depression increases (41% vs. 59%). At T2, there was a return to baseline levels and a progressive decrease in the following evaluations (Table 2).

No concomitant medications were reported.

3.7. Psychological distress persistence

3.7.1. Anxiety

To highlight persistent anxiety, the number of patients that continuously experienced anxiety levels ≥8 from T0 to T6 was calculated.

At T0, a total of 47 (60%) patients experienced anxiety, and among these anxiety persisted in 44 (56%) at T1, in 39 (55%) patients at T2, in 31 at T3 (44%), in 26 (40%) patients at T4, in 16(26%) at T5 and in 13(23%) at T6 (Fig. 3).

3.7.2. Depression

To highlight persistent depression, the number of patients that continuously presented depression levels ≥8 from T0 to T6 was calculated.

At T0, a total of 41 (53%) patients showed depression, and at T1 40 (52%), at T2, T3,T4, T5, T6 depression continued in 34 (48%), 29 (41%), 24 (37%), 13 (21%), 11 (20%) patients respectively (Fig. 3).

3.7.3. Anxiety and depression associated with CRF

At T2, T3, T4 the persistence of anxiety associated with CRF was observed in 15 (20%), 8 (11%) and 3 (5%) patients, respectively.

At T2, T3, T4 the persistence of depression and CRF was showed in 11(15%), 7 (10%) and 3 (5%) patients, respectively.

3.8. The course of QoL

As shown in Fig. 4, all variables of QoL highlighted a deterioration at T1, T2 and T3, regardless of baseline scores, and then gradually improved until to reaching higher scores than those in the baseline at follow-up of 5 and 10 years.

3.9. Clinical and psychosocial factors related to CRF

3.9.1. CRF and psychological distress

In patients with CRF levels <36, anxiety and depression scores varied compared to non-fatigued patients. At T0, 57% (4/7) of patients with fatigue had anxiety scores ≥8 in contrast with 60% of non-fatigued patients (43/71), at T1 74% patients (28/38) vs. 55% (22/40) (p = 0.01); at T2 66% (23/35) vs. 50% (20/40), at T3 64% (14/22) versus 57% (28/49), at T4 75% (6/8) vs. 52% (30/57).

At T0, 43% (3/7) of patients with fatigue <36 had depression scores higher than 8 vs. 53% of non-fatigued patients (38/71), at T1 66% (25/38) vs. 53% (21/40) (p = 0.05), at T2 57% (20/35) vs. 55% (22/40), at T3 55% (12/22) vs. 45% (22/49), at T4 87% (7/8) vs. 40% (23/58).

This finding is also confirmed by the MCA showing that at T1 a clear difference between patients with and without CRF compared to psychological distress: patients with CRF scores <36 are also those with anxiety and depression borderline (8−10) and pathological scores (≥11) Fig. 5.

3.9.2. CRF and QoL

In regards to the relationship between Qol and CRF, higher baseline CRF levels are associated with lower global Qol (60 vs. 73 p: 0.01), physical (70 vs. 84 p: 0.003) and role functioning (68 vs. 84 p = 0.02). At T1 the impact of CRF affects all Qol areas (p < 0.05), except for social and cognitive functioning, at T2 affects all Qol areas (p < 0.05) with the exception of cognitive functioning, at T3 it affects only social (61 vs 75 p = 0.01), physical (73 vs. 81 p: 0.04) and role functioning (70 vs 81 p: 0.03). The greatest impact is observed at T2.

3.9.3. CRF and clinical features

We studied CRF in association with the patients clinical characteristics including: menopausal status, age, drug-including chemotherapy, toxicity (grade 2-3-4 anemia, neutropenia and neurotoxicity) and the adjuvant HT following CT.

Table 2
The course of psychological distress.

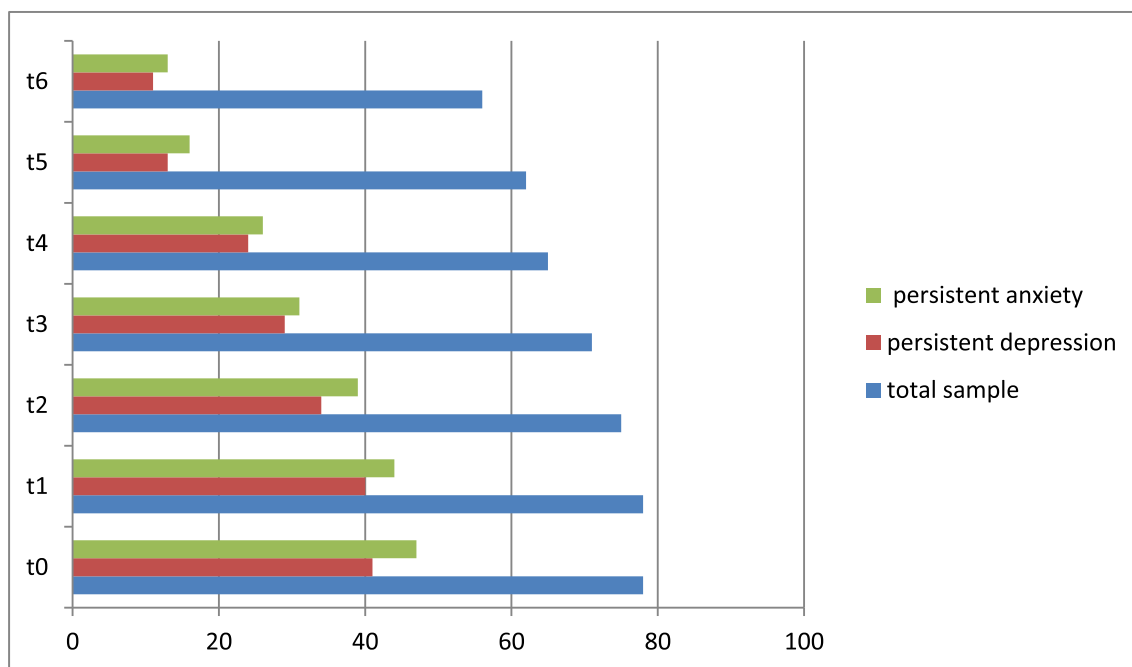|	% Anxiety 0−7	% Anxiety 8−10	% Anxiety >10	% Depression 0−7	% Depression 8−10	% Depression >10
Baseline	40	46	14	47	38	15
T1	36	49	15	41	44	15
T2	43	43	14	44	41	15
T3	41	45	14	52	34	14
T4	45	38	16	55	30	15
T5	54	35	11	57	35	8
T6	54	38	8	60	31	9

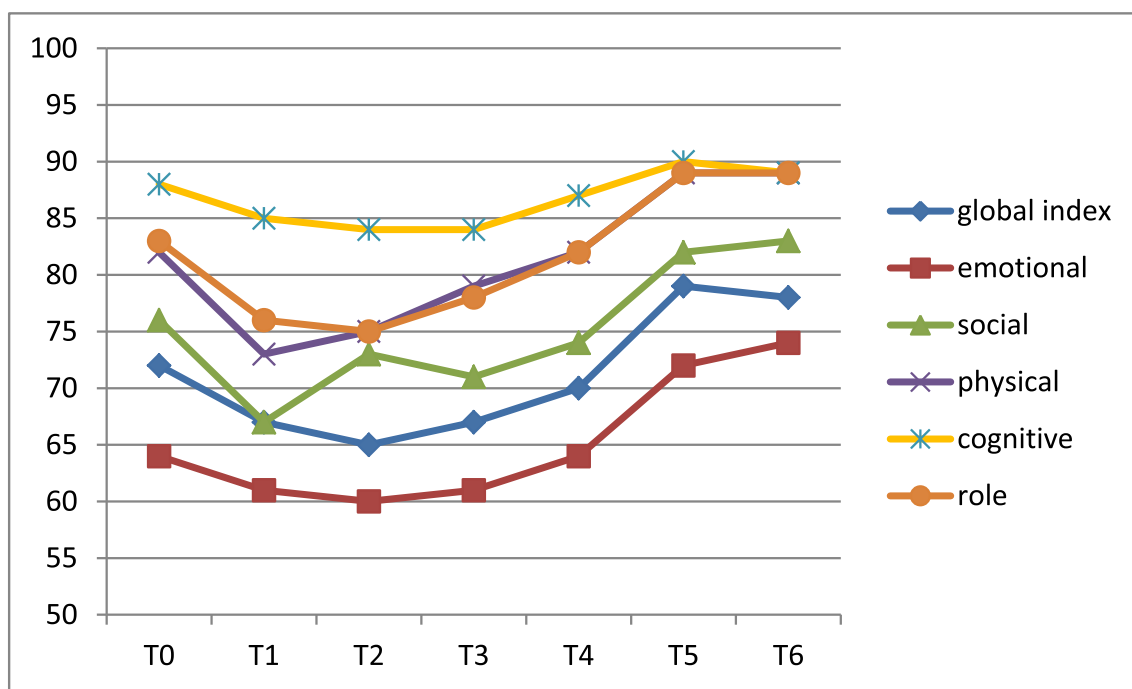**Fig. 3.** Psychological distress persistence.

Fig. 4. The course of Quality of Life.

Forty-one and 37 patients at baseline presented premenopausal and postmenopausal status, respectively. During the time of treatment, 16 (39%) and 22 (59%) patients in pre and post menopausal status, respectively showed CRF (p = 0.07). At T3, 14 (42%) postmenopausal patients presented a significantly higher CRF (<36 value) than 8 (21%) pre-menopausal patients (p = 0.05). At T5 and T6, the two groups of patients presented no differences.

No differences were observed in the other factors investigated. Only a trend in patients with peripheral neurotoxicity in the course of taxane-containing adjuvant CT was observed (p = 0.07).

4. Discussion

Despite growing interest on behalf of the researchers in CRF and in understanding this phenomenon, little is known about the course of CRF along the cancer trajectory and about the clinical, psychological and demographic risk factors, which could predict CRF development and persistence in survivors.
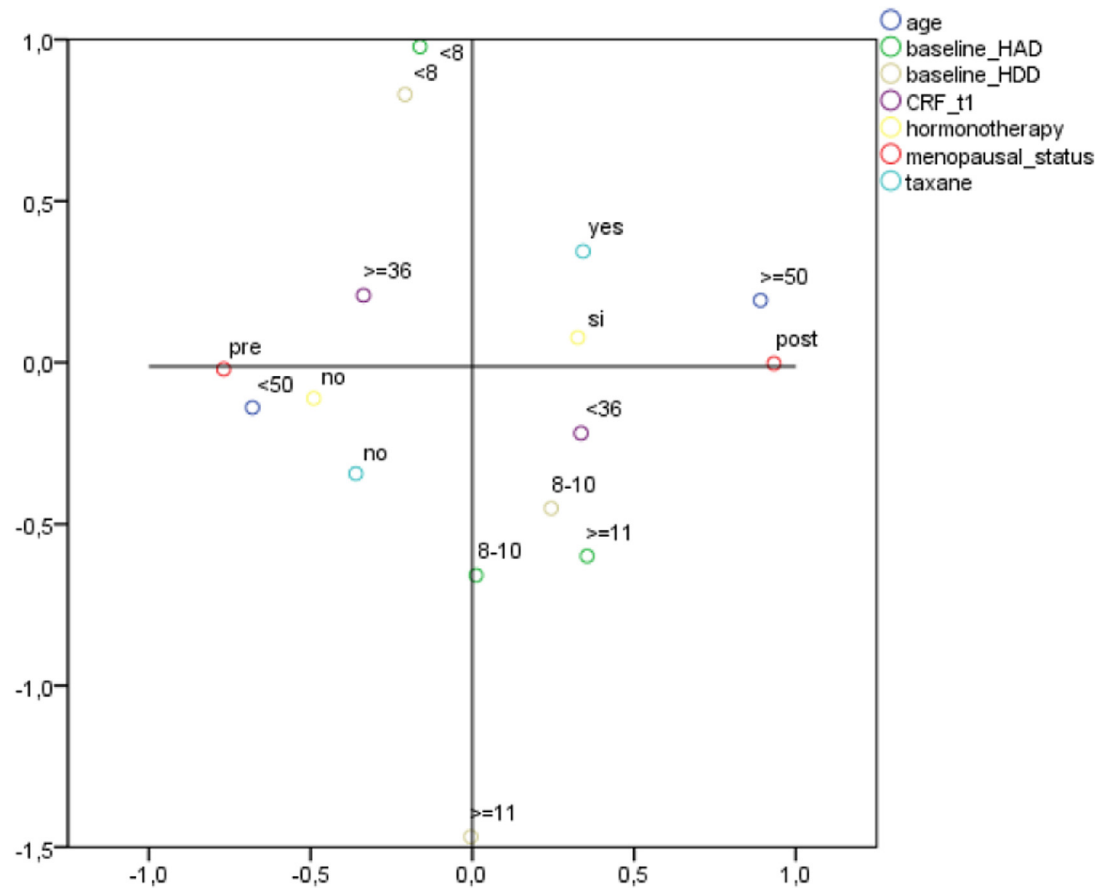
Fig. 5. Multiple Correspondence Analysis: CRF at time t1 in relations to some patient' s features at time t0.

The few prospective studies on treating fatigue in BC patients [1,17,21,22,34,47] reported a wide range in the incidence rate of CRF during the course of the disease mainly due to the heterogeneity of treatments, the timing of assessment, the tools used and also the failure to use the full set of criteria identified in the definition of CRF [48].

Our prospective, longitudinal study, detected the CRF trajectory from the surgery to ten years of follow-up.

On the basis of the cut-off rate of 36, clinically significant fatigue levels were identified after surgery (9%). These levels increased during (49%) and at the end of the treatments (47%), and continued to persist after 1 year (31%) and declined in the subsequent time up to ten years of follow-up.

CRF incidence after surgery, according to Andrikowsly et al. [47], may be motivated by factors related to the tumor and/or by high levels of physical and psychological stress related to the cancer diagnosis and to the surgical treatment outcomes.

Compared to other prospective studies, prevalence of CRF in our sample was higher at the end of adjuvant systemic therapies and lower in follow-up [34], probably due to cumulative side effects of the entire chemotherapy, also if not so high grade and incidence of side effects were observed. We must take into consideration that the study started about fifteen years ago and the supportive care for antiemetics prophylaxis, the management of neutropenia prevention were not available and a better definitions of toxicity grading reported by the oncologists were not so applied. Furthermore patient reported outcome was not adopted, and all toxicity felt by the single patient was reported objectively by the physician, with a possible bias of real side effect due to therapy. In an era in which supportive care represents a significant end point of cure, it is

needed to assess the CRF patient perception in the global side effects both in the course of oncological treatment and follow-up.

Increased CRF prevalence during CT could be also attributed to the use of only a subset of CRF definition criteria [49].

It is interesting to note that the prevalence of fatigue detected through the FACT-F is lower than that reported by the patient according to the subjective perception of the condition that most impacts the daily functioning over time. As noted in the literature, FACT-F may underestimate the number of patients with significant levels of CRF [15].

CRF is a common condition that mostly impacts daily functioning on 58% of patients during CT treatment and 43% of patients at the end of the CT. It is not surprising that CRF 1 year from CT is considered to impact only 14% of patients, indicating overcoming the effect determined by CT.

The design of most studies on CRF in BC patients allowed to detect CRF levels but not its duration, that has been defined as the third dimension [20], making it impossible to distinguish between patients with transitory and persistent CRF.

This is especially relevant in the population of survivors for identifying high risk patients needing targeted interventions.

In agreement with the results by Goldstein [34], our study found CRF persists for 12 months or more after the end of CT treatment in 32% of patients.

The study also showed that at the end of CT the persistence of CRF is associated with persistent anxiety and depression, respectively in 20% and in 15% of patients, at 12 months from the end of CT in 11% and 10%, and at 2 years of follow-up in 5% of patients.

To date, there is little information available on the behavioral pattern of CRF from treatment until survivorship phase.

The direction of CRF, according to SCIDs, showed at the end of the CT persistent fatigue in 57% of patients (stability/worsening), incident fatigue in 29%, and transient fatigue in 29% of women. A subset of patients (14%) who remain fatigued was also detected despite their scores in the improving category (score <36). In the time following, the percentage of transient fatigue increases, persistent fatigue remains stable and incident fatigue decreases. This trend seems to indicate the temporal relationship between CRF and CT period. The cases of incident fatigue are depleted within one year from completing CT and only 3% patients showed fatigue at 5 years from CT.

The presence of CRF in 5% of patients at 10 years from the end of CT may underline the role played by other factors, such as the onset of new stressful life events and the comorbidities associated with aging.

It is interesting to note that the analysis of clinical, psychological and demographic characteristics of patients with significant fatigue, has detected only the presence of reactive or pathological anxiety and depression.

This analysis if extended to a larger sample could highlight specific subgroups of patients, characterized by a constellation of clinical, demographic and psychosocial variables that define different risk conditions. This would allow not only to stratify patients in clinical trials but also to target interventions to improve CRF and psychological distress according to the risk level.

Our study confirm previous studies [50–52] which underline the "roller coaster effect" with a significant increase in levels of fatigue immediately after infusion.

As to the QoL over time, we observed worsening during the end and at 1 year of CT, and an improvement in the period of time thereafter. This last observation may possibly reflect the process of patient adaptation. Various explanations have been given for the presence of a good quality of life in long-term survivors. One explanation could be the concept of reframing/shift [53] in response which we hypothesize that BC survivors either establish a new meaning of the concept of QoL or change their own internal standards as a result of adaptation to the limitations associated with the disease or its treatment. Another reason for a good QoL could be the finding of any type of benefit arising from the cancer experience, known as benefit finding or post-traumatic growth [54]. Anxiety and depression, according to the QoL trend, showed the presence of a reactive/pathological disorder during and at the end of CT and at 1 year from the end of adjuvant systemic treatment and a return to normality scores in the period of time thereafter.

In regards to the relationship between CRF and Qol, several studies have shown a lower Qol in fatigued patients and the negative effects of CRF on daily functioning during CT and in BC survivors [1,27].

It was further highlighted that this relationship could justify the poor compliance to CT regimens and discontinuation of therapy, thus underlining the importance of CRF improvement interventions in this category of patients [19,28–30].

According to these studies the most impacted areas in our sample are those related to the daily functioning (physical and role functioning).

As far as the relationship between CRF and psychological distress, our study showed that, since the CRF onset up to 24 months of follow-up, the patients with CRF scores <36 had anxiety and depression scores higher than the cut-off of 8 in the same evaluation, indicating a relationship between the presence of CRF and the presence of psychological distress. Graphics representing multiple correspondence analysis evidence the significant relationship between baseline scores of anxiety and depression => 8 (HADS) and CRF scores (FACT-F <36) during adjuvant treatment and in the following evaluations indicating that women presenting

reactive and pathological depression and anxiety before CT treatment are at risk for the onset of fatigue in a later period. Directionality between CRF and mental state is still difficult to confirm due to lacking data regarding fatigue before illness as well as our small sample that prevents carrying out further statistical analysis.

Our study supports those studies that do not detect a relationship between CRF and factors related to the disease and treatment [6,18,55]. The observed trend between CRF and both postmenopausal status and peripheral neurotoxicity underline the impact on fatigue of these two factors ($p = 0.07$).

The ability to determine the predictors of trajectory of fatigue during and after CT could make way for preventive strategies on the management of patients who are at greater risk of fatigue.

The strength of our study lies in the prospective and long-term CRF view, and in its quantitative and qualitative analysis within a homogeneous sample. The prospective longitudinal design of the study permits to identify the CRF incidence rate, timing of onset, duration, and the impact on QoL.

Despite these strengths, the study also has its limitations.

The small of sample size and its reduction over time do not allow a subgroup analysis. CRF incidence is conditioned by the use of only some criteria established for adequate definition of CRF, preventing to be able to obtain a comparison and a clear interpretation of the results. A shared definition of fatigue promotes the understanding of its etiology and the development of evidence-based approaches to address it.

Moreover, while the choice of HADS as a psychological distress evaluation tool showed characteristics of higher specificity than the FACT-F and less contamination of is relationship with CRF, the choice of FACT-F recognizes certain limits. According to our opinion, its use appears to be more appropriate in clinical practice and into intervention studies rather than in the research. Furthermore, the choice of a cut-off for discriminating between cases and non-cases while accounting for CRF severity, does not consider CRF characteristics that bear clinical significance. In addition, the instrument's low specificity producing a high number of false negatives could reduce the generalizability of the study results. Thus, a diagnostic interview is required.

The absence of a CRF assessment before the onset of disease and the absence of a control group makes it difficult to clearly determine whether the CRF is linked to diagnosis and treatment for cancer as well as to identify common and specific predictors of CRF in cancer survivors and in healthy women. Several studies however, found a lower prevalence of fatigue (12–22%) in the general population than in BC women after treatment [21].

Furthermore, although women with certain comorbidities linked to significant fatigue symptoms were excluded from study, we did not assess the onset of physical comorbidity over time. Such comorbidities can affect the experience of fatigue and ideally should be included as control variables in future analyses comparing patients with CRF and those without.

Overall, the findings of the current study suggest that the persistence of fatigue is experienced by a minority of women treated with chemotherapy followed or not by hormonal therapy for early BC. The Identification of biological and psychological CRF targets could be significantly helpful for early interventions in a subset of patients who are at more risk of developing fatigue.

Conflict of interest

manuscript and decided to submit the manuscript for publication.

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