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Research

Fatigue Syndrome in Patients with Bone and Soft Tissue Sarcomas: An Observational Study

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ABSTRACT

Objectives: The aim of the present study is to describe the course of fatigue syndrome in patients with musculoskeletal tumors starting from chemotherapy and to compare it with that of other cancer populations. The second objective is to identify the risk factors for a higher level of fatigue.
Methods: A prospective prognostic observational cohort study was carried out. All patients diagnosed with musculoskeletal tumors who started chemotherapy treatment over 12 years of age were identified and enrolled consecutively from July 2019 to April 2021 in the osteo-oncology department. Patients' fatigue was measured using the Brief Fatigue Inventory at four different time points: at the beginning of treatment and then subsequently at 6, 12 and 24 months from the time of enrollment.
Results: The mean fatigue value was 3.3 (SD = 2.4) at the start of antiblastic treatment, which progressively decreased over time until it reached a mean score of 2.1 (SD = 1.5). At 24 months; 17% of patients had moderate/severe fatigue. Presence of metastases at the onset of the disease, location of the tumor in the upper limb, a shorter oncological treatment-free gap and surgical treatment were independent predictive factors of BFI score.
Conclusion: In patients with musculoskeletal tumors, fatigue is a complication of the disease itself and does not occur only after chemotherapy treatment. In the first two years of treatment, there is a decreasing trend in fatigue syndrome, which remains a significant complication to be monitored over time and to be considered in patient management. Prevention pathways should be implemented.
Implications for Nursing Practice: During chemotherapy treatment of patients with bone and soft tissue sarcomas, a fatigue prevention plan should be implemented. Patients with tumor localisation in the upper limb, metastasis at onset and surgical treatment have a higher risk of developing a higher fatigue score.

Fatigue syndrome in cancer patients is recognized as one of the most common and difficult adverse events to manage,[1-4] especially for patients undergoing chemotherapy treatment.[5-9] In the literature the prevalence of fatigue syndrome can vary from 14% to 100% according to the different rating scales used and the different types of cancers investigated.[10] The impact of this syndrome on patients' quality of life is well shown and requires adequate management by healthcare professionals.[1,11]

At present, the assessment of fatigue has been poorly described in patients with musculoskeletal tumors. This type of tumor requires a specific treatment approach due to its unique characteristics compared to other types of tumors.[12,13] Firstly, patients often undergo resection and reconstruction of the musculoskeletal system, which restricts physical activity and may influence the onset of fatigue syndrome. Secondly, treatment varies according to the wide range of types of bone and soft tissue tumors, which require different therapeutic approaches. These might involve the use of radiotherapy and prolonged periods of treatment.

Aksens et al.[12] suggested that patients with malignant bone tumors of the extremities should be informed of the risk of fatigue syndrome as an adverse event of treatment and should be prepared to manage limited physical activity. No data are available on the possible risk factors of fatigue syndrome in this specific population. The risk factors for fatigue highlighted in a meta-analysis performed on a nonspecific cancer population were: limited physical status, chemotherapy treatment, female sex, insomnia, neurosis, pain and depression.[10] Knowing specific risk factors for patients with

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Layperson Summary

What we investigated and why

During chemotherapy treatment, fatigue is a common complication for patients. Currently, fatigue assessment has been poorly described in patients with musculoskeletal tumors. This type of tumor requires a specific therapeutic approach due to its unique characteristics compared to other tumor types. Patients with bone tumors are often treated with a surgical approach that can lead to significant limitations in autonomy and walking.

How we did our research

Patients were followed up from the start of chemotherapy treatment for bone and soft tissue sarcoma and the fatigue syndrome was assessed over time for 2 years. We collected patient data to identify patients who are likely to have a higher fatigue score.

What we have found

Fatigue syndrome is a moderate/severe condition for 17% of patients with bone cancer. Fatigue is a complication of the disease itself and does not only occur after chemotherapy treatment. Patients with tumor localisation in the upper limb, metastases at onset and surgical treatment have a higher risk of developing a higher fatigue score.

What it means

During chemotherapy treatment of patients with bone and soft tissue sarcomas, fatigue should be evaluated in regular clinical practice. A fatigue prevention plan should be implemented from the start of treatment. Patients at high risk of developing a higher fatigue score should be monitored more carefully.

musculoskeletal tumors is necessary to identify patients prone to this adverse event and to propose more effective ways of managing fatigue.

The aim of the present study is to describe the course of fatigue syndrome in patients with musculoskeletal tumors starting from chemotherapy and to compare it with that of other cancer populations. The second objective is to identify the risk factors for a higher level of fatigue.

Material and Methods

Study design: Prospective prognostic observational cohort study. The study was approved by the Ethics Committee, number 437/2019/OSS/Ior (19/06/2019), and registered on clinicaltrial.gov, number NCT04104750 (26/09/2019).

Population: the study was performed in the osteoncology department of a hospital specialized in the treatment of musculoskeletal tumors. Informed consent was obtained from participants during their initial hospitalization when the first intravenous antiblastic drug was administered. Patients eligible for participation in the study were identified and enrolled consecutively according to the inclusion and exclusion criteria described below from July 2019 to April 2021.

Inclusion/Exclusion Criteria: All patients diagnosed with musculoskeletal tumors who started chemotherapy treatment over 12 years of age. Only patients with a poor knowledge of the Italian language that prevented a correct understanding and compilation of the rating scales were excluded from the study.

Outcome: Patients' fatigue was measured at four different time points: at the beginning of treatment and then subsequently at 6, 12 and 24 months from the time of enrollment. The Brief Fatigue Inventory (BFI) was used for the assessment of fatigue syndrome.[14-16] This scale consists of 9 items:

– 3 items measure the severity of fatigue “now”, “usual” and “worst” during past 24 hours, with 0 being “no fatigue” and 10 being “fatigue as bad as you can imagine.”

– 6 items assess the interference of fatigue during the past 24 hours with different aspects of the patient’s life, as general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life, with 0 being “does not interfere” and 10 being “completely interferes.”

Total score ranging from 0 to 90 and the measurement was reported as the mean score of all items. Based on the score, the level of fatigue was divided into absent/mild for scores below 3 and moderate/severe for scores greater than or equal to 4.[15,17]

Variables: any predictors of fatigue syndrome were identified through a literature search and consultation with professionals from different disciplines (nurses, physiotherapists, oncologists, orthopedists). The variables tested were: age, sex, body mass index, smoking, location of the tumor (upper limb, lower limb or other site), presence of metastases at the time of diagnosis, type of tumor (differentiated according to treatment administered: soft-tissue or other type of sarcoma vs osteosarcoma/Ewing sarcoma), initial patient status measured by the NRS pain scale and functional ability using the Toronto Extremity Salvage Score (TESS). NRS pain is an 11-point scale scored from 0 to 10, where 0 is ‘no pain’ and 10 is ‘the most intense pain imaginable’. Patients verbally selected the value most in line with the intensity of the pain they experienced in the last 24 hours. TESS measures the patient’s perception of their ability to perform 30 activities of daily living ranging from 1 (impossible to perform) to 5 (not at all difficult). The score was normalized from 0 to 100 where a higher score indicated better functional ability.[18,19] For the purpose of the present study, the lower limb version of the TESS was used for all patient regardless of tumor location. Treatment pathway, such as any surgical treatment and the conclusion of treatment pathway and the number of months elapsed between the end of treatment and 24-month follow up.

All variables and BFI were collected by direct interview with the enrolled patients and the consultation of clinical documentation collected by the nurses working at the osteo-oncology department.

Sample size: in accordance with the general rule of thumb that for each prognostic factor included in a multivariate model it is necessary to have 15 events for the analysis of a continuous outcome, a number of 100 patients allowed 6/7 variables to be included together in the model, thus limiting the risk of producing extreme effect estimates.

Statistical analysis: Statistical analysis was performed using SPSS v20 software (IBM Corp. Armonk, NY, USA). Data were described by mean and standard deviation values for continuous variables and absolute number and percentage values for dichotomous variables. Univariate analysis between the individual variables and the 24-month BFI score was performed using the Pearson coefficient for continuous variables and the t-test for comparison of the means of the dichotomous variables. Variables with a statistical significance level of less than 0.157 were considered for multiple analysis. The Generalized Linear Model was used to evaluate possible confounders through multiple analysis.

Results

The number of patients referred to the osteoncology department in the study period was 152. According to the inclusion and exclusion criteria, there were 103 eligible patients, of which 101 were enrolled. At the subsequent 6-, 12- and 24-month follow-ups, the assessment

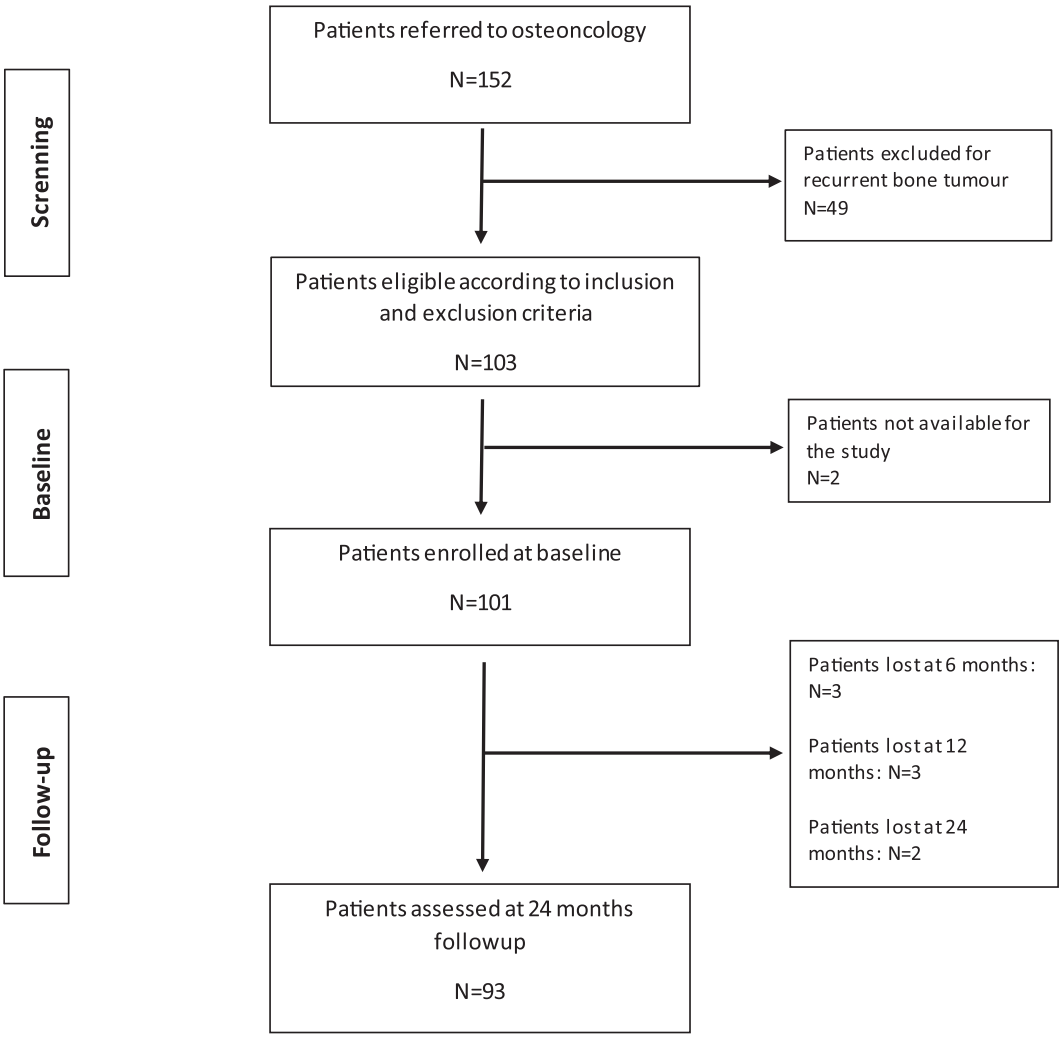

Fig. Flow diagram.

of fatigue was possible in 98, 95 and 93 patients, respectively. The flow of patients is summarized in Fig. The mean age of patients was 42.1 years (SD=19.8) and 36.6% were women. Table 1 summarizes the baseline characteristics of the sample and the univariate analysis between the different variables examined and the BFI score of the patients at 24 months. It should be noted that on average the percentage of patients who underwent surgery was high at 86%, antiblastic therapy lasted about 12 months and that at 24 months 19% of patients were still being treated following disease progression or relapse.

The mean fatigue value was 3.3 (SD = 2.4) at the start of antiblastic treatment, which progressively decreased over time until it reached a mean score of 2.1 (SD = 1.5). Anova test for repeated measures revealed a significant effect of time on BFI score ($F(3, 92) = 4.94$, pvalue = 0.003). At 24 months; 17% of patients had moderate/severe fatigue (Table 2). Comparing the BFI scores obtained with the values presented by other studies that considered different types of tumor (Table 3), there was a similar percentage of patients with moderate/severe fatigue, equal to 16.8% and 18.3% respectively for patients with lung and breast cancer. For populations where different types of tumors were considered, the percentage of patients with moderate to severe syndrome was more than 40%.

Univariate (Table 1) and multiple (Table 4) analyses showed that the risk factors that had a statistically significant independent association with the BFI score at 24 months were: the presence of metastases at the onset of the disease; the location of the tumor in the upper limb; a shorter oncological treatment-free gap; and surgical treatment. Patients with upper limb tumors had higher mean fatigue values (3.3; DS=1.8). A further descriptive analysis of the main baseline characteristics and course of fatigue was conducted by stratifying patients according to diagnosis (bone tumor/Ewing's sarcoma vs. soft tissue tumors) (Table 5). Clinically significant differences emerged with respect to age, the number of patients diagnosed with metastases at onset and their functional capacity. In relation to fatigue syndrome, patients with bone tumors had a higher mean BFI than patients with soft tissue tumors (3.8 vs 3.0) and this difference gradually decreased over time (2.2 vs 2.1).

Discussion

Fatigue syndrome is an issue that needs to be addressed at the beginning of chemotherapy treatment for patients with musculoskeletal tumors. The BFI score was at its peak at the beginning of treatment and then showed a progressive mean decrease over the following two years but, since it was severe in 17% of patients, it should still be considered as a possible adverse event. Fatigue syndrome screening and patient education should be encouraged in clinical practice from the first chemotherapy treatment even for patients with bone and soft tissue tumors. The present data confirm the importance of focusing on this problem over time, even after the end of treatment. Exercise treatment has been shown to be effective in managing fatigue syndrome during and after chemotherapy.[20,21]

Table 1
Baseline Characteristic of Sample and Univariate Analysis

Categorical Variables		N (93)	BFI score- 24 Months	*P* value
Age (years), n (%)	12-18	17 (18.3)	1.9 (1.9)	.073
	19-30	13 (14.0)	1.4 (1.2)	
	>30	63 (67.7)	2.4 (1.4)	
Sex, n (%)	Female	34 (36.6)	1.7 (1.3)	.037
	Male	59 (63.4)	2.4 (1.6)	
Smoker, n (%)	Yes	14 (15.1)	2.6 (1.4)	.277
	No	79 (84.9)	2.1 (1.5)	
Site of tumor, n (%)	Upper limb	18 (19.8)	3.3 (1.8)	.001
	Lower limb	54 (59.3)	2.0 (1.3)	
	Other	19 (20.9)	1.5 (1.2)	
Early onset metastasis, n (%)	Yes	32 (34.4)	2.6 (1.6)	.038
	no	61 (65.6)	1.9 (1.5)	
Diagnosis, n (%)	Soft-tissue or other type of sarcoma	57 (61.3)	2.2 (1.6)	.880
	Osteosarcoma or Ewing sarcoma	36 (38.7)	2.1 (1.3)	
Surgery, n (%)	Yes	80 (86.0)	2.2 (1.6)	.107
	no	13 (14.0)	1.5 (1.1)	
Chemotherapy treatment at 24 months, n (%)	yes	17 (18.9)	2.7 (2.3)	.090
	no	73 (81.1)	2.0 (1.7)	
Continuous variables		Mean (SD)	PCC	*P* value
Body Mass Index, mean (SD)		24.6 (5.6)	−0.044	.675
TESS score, mean (SD)		66.4 (27.3)	0.066	.532
Pain Score, mean (SD)		2.8 (2.4)	−0.064	.543
BFI Score, mean (SD)		3.3 (2.4)	−0.203	.051
Free months from the end of chemotherapy treatment, mean (SD)		11.8 (7.6)	−0.208	.049

BFI, Brief Fatigue Index; PCC, Pearson correlation coefficient; SD, standard deviation; TESS, Toronto extremity salvage score.
Missing: 2 for site of tumour, 3 for surgery, 3 for conclusion of chemotherapy treatment at 24 months and 3 for free months from the end of chemotherapy.

Table 2
BFI Score Trend from Baseline to 24 Months of Follow-Up

		Follow-up		
	Baseline (N=101)	6 months (N=98)	12 months (N=95)	24 months (N=93)
BFI Score, mean (SD)	3.3 (2.4)	2.8 (2.2)	2.4 (2.0)	2.1 (1.5)
Moderate/Severe Fatigue, n (%)	39 (38.6%)	35 (35.7%)	19 (20%)	16 (17.2%)
Absent/Mild Fatigue, n (%)	62 (61.4%)	63 (64.3%)	76 (80%)	77 (82.8%)

BFI, Brief Fatigue Index.

Table 3
Literature Review About Fatigue in Patients with Bone and Soft Tissue Sarcomas

Author	N	Type of tumor	Age / Sex	Follow-up	Fatigue
Servaes, 2003	170	Benign and Malignant Bone Tumors	Benign: 34 Malignant: 43 47% female	Cancer-free 3.3aa	CIS 28% severe
Aksnes, 2007	57	Mixed cancer	Mean, 18 yrs 46% female	Cancer-free 12.5 aa	FQ: 14% chronic fatigue
Hung, 2011	350	Lung cancer	68.8 yrs 63.4% female	Cancer-free	BFI 16.8% mod/sev
Tan, 2014	180	Breast cancer	53.8 yrs n.a.	2.1 aa	BFI 18.3% mod/sev
Di Marco, 2018	48	Pancreatic cancer	62.6% >65year 39.6% female	During cancer treatment	BFI 2.8 points 39.6% mod/sev
Iwase, 2015	185	Mixed cancer	63.5 yrs 38.8% female	57.9% cancer free 4 months from diagnosis	BFI 59.5 % mod/sev
Tian, 2016	1749	Mixed cancer	56.9 yrs 49.6% female	27.8% cancer-free	BFI 52.1% mod/sev
Roila, 2018	1394	Mixed cancer	81.1% >50yrs 58.3% female	22.6% cancer-free	BFI 62.1% mod/sev

BFI, Brief Fatigue Index; CIS, checklist individual strength; FQ, fatigue questionnaire; n.a., not available; yrs, years.

Table 4
Multiple Linear Regression Analysis of BFI Score At 24 Months

		B	95% CI	*P* value
Site of tumor	Upper limb	1.904	1.056; 2.752	<.001
	Lower limb	0.845	0.166; 1.524	.015
Early onset metastasis		0.616	0.041; 1.190	.036
Free months from the end of chemotherapy treatment		-0.054	−0.091; - 0.018	.003
Surgery		0.815	0.001; 1.629	.050

Table 5
Baseline Characteristic and BFI Score Trend for Bone vs Soft Tissue Tumor

		Bone tumor / Sarcoma of Ewing (N=36)	Soft tissue tumor / other sarcoma (N=57)
Age, mean (SD)		32.3 (19.1)	48.3 (17.7)
Sex, n (%)	Female	15 (41.7)	19 (33.3)
	Male	21 (58.3)	38 (66.7)
Site of tumor, n (%)	Upper limb	6 (17.1)	12 (21.4)
	Lower limb	20 (57.1)	34 (60.7)
	Other	9 (25.7)	10 (17.9)
Early onset metastasis, n (%)	Yes	6 (16.7)	26 (45.6)
	no	30 (83.3)	31 (54.4)
TESS score, mean (SD)		59.9 (30.4)	70.6 (24.5)
Pain Score, mean (SD)		2.8 (2.3)	2.7 (2.4)
Surgery, n (%)	Yes	31 (86.1)	49 (86.0)
	no	5 (13.9)	8 (14.0)
Free months from the end of chemotherapy treatment, mean (SD)		10.7 (6.6)	12.5 (8.2)
BFI score	Baseline	3.8 (2.6)	3.0 (2.3)
	6 months	2.9 (2.3)	2.7 (2.1)
	12 months	2.3 (2.2)	2.4 (1.9)
	24 months	2.2 (1.5)	2.1 (1.6)

BFI, Brief Fatigue Index; SD, standard deviation; TESS, Toronto extremity salvage score.

Recovery of autonomy and motor performance is a key component of patients with bone cancer and soft tissue sarcomas, particularly after surgical resection operations that are performed. For this type of patient, the exercise must be adapted to the specific motor skills of the patient.

It can be hypothesized that for patients suffering from musculoskeletal tumors, the initial fatigue syndrome is mainly linked to pain and limitations in mobility and physical activity brought about by the disease itself and then surgery in the first phase of treatment. As the months go by, the improvement in pain, mobility and young age might mitigate the negative effects of chemotherapy treatment in the onset or chronicity of fatigue. Studies with a longer follow-up are needed to verify if this decreasing trend can be confirmed over time or whether fatigue becomes chronic in some of the patients. The latter hypothesis seems to be supported by studies by Aksens (2007) and Servaes (2003) who showed that the rate of people affected by fatigue syndrome was respectively 14% and 28% with prolonged follow-up periods in disease-free subjects. However, when making comparisons with these two studies, it should be remembered that different fatigue assessment tools were used and the fact that they are older studies when bone cancer treatment methods were at least partly different.

In other types of cancer, where fatigue assessment was carried out using the BFI, this syndrome was more marked and relevant, ranging from 16% to 62% of patients with a moderate/severe level of fatigue. This difference might be explained by the basic characteristics of the populations studied, regardless of the different cancer diagnosis. The studies in which the lowest rates of severe fatigue were reported were those in which the study population was free of the disease. In contrast, studies in which a percentage of patients were still on treatment had higher fatigue rates.

The same trend was observed for the population of the present study, if we look at the data relating to the first follow-up, where almost all patients were still undergoing chemotherapy treatment, the highest percentages (35.7%) of fatigue syndrome were found. A second difference was the average age of the patients enrolled: patients with musculoskeletal tumors were younger on average. Different number of patients enrolled must also be taken into account. The studies by Tian et al. and Roila et al., in which different tumor types were considered, had very large populations. The low prevalence of bone tumors makes studies with such large numbers difficult and, at the same time, the specific characteristics of these patients require dedicated studies to bring out the peculiarities of these tumors, which might otherwise remain unnoticed. For musculoskeletal tumor patients, the independent risk factors for fatigue intensity were the presence of metastases at the beginning of chemotherapy treatment, a shorter cancer-free treatment time, resection and reconstruction surgery, and the localization of the tumor. The latter two factors are specific for this type of patient and underline the need for a special analysis for this group of cancer patients where chemotherapy and surgical resection treatment are two closely related elements. Patients with tumor located in the upper limb had a mean BFI score of 3.3, which was 1.3 points and 1.8 points higher, respectively, than patients with tumors located in the lower limbs and other sites. Location in the upper limb might be the reason for reduced motor performance in activities of daily living for bone tumor patients[22,23] and therefore also facilitate higher levels of fatigue. Reduced motor performance and chemotherapy treatment were among the risk factors that emerged from the review by Ma et al.[10] in relation to fatigue syndrome and are therefore supported by the data of the present study. Patients who had completed chemotherapy treatment had a BFI score of 0.7 points lower and the level of fatigue decreased along with the time that elapsed after treatment. The trend in BFI scores for patients with bone cancer showed higher values at the start of treatment than for patients diagnosed with soft tissue cancer. In both groups, the mean BFI decreased gradually over the two years of observation until a similar score was reached.

Limits

First of all, the sample size was small, making the analysis of some subgroups less consistent, such as the different types of diagnoses. The rarity of bone tumors makes it difficult to have a large sample size. The population studied was in line with similar studies by Aksens and Sevaes with populations of 57 and 170 patients, respectively. It was also found that patients with bone tumors need a specific assessment and their characteristics do not emerge in large-sample studies on populations that include various types of tumor. In addition, further studies are needed to assess fatigue with prolonged follow-up over time to understand the effects of oncological pathology and related therapies in the long term. A second study limit is the failure to collect radiotherapy and certain values from patients' blood tests that might be associated with fatigue such as hemoglobin level and red blood cell count. It is assumed that these factors may have a greater association during chemotherapy treatment whereas in relation to fatigue syndrome two years after the start of treatment the effect may be limited.

Conclusions

In patients with musculoskeletal tumors, fatigue is a complication of the disease itself and does not occur only after chemotherapy treatment. In the first two years of treatment, there is a decreasing trend in fatigue syndrome, which remains a significant complication. Fatigue syndrome screening and patient education should be encouraged in clinical practice from the first chemotherapy treatment.

Patients with upper limb tumors, the need for surgical treatment, prolonged chemotherapy treatment and the presence of metastases are at greater risk of developing a significant level of fatigue over time and more articulated monitoring and prevention pathways should be implemented in these patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Mattia Morri: Writing – original draft, Methodology, Formal analysis. **Riccardo Boccomino:** Investigation, Formal analysis, Conceptualization. **Eugenio Brruku:** Investigation, Data curation, Conceptualization. **Ausilia Bellina Terra:** Investigation, Data curation, Conceptualization. **Rita Boschi:** Investigation, Formal analysis, Conceptualization. **Giovanni Raucci:** Investigation, Data curation. **Daniela Sabbi:** Investigation, Data curation, Conceptualization. **Toni Ibrahim:** Writing – review & editing, Supervision, Formal analysis. **Paola Coluccino:** Writing – review & editing, Supervision, Investigation, Formal analysis, Data curation, Conceptualization.

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