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RESEARCH ARTICLE

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COMT genotypes correlate with cancer-related fatigue in breast cancer survivors

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ABSTRACT

Purpose: Cancer-related fatigue (CRF) is the most common and debilitating symptom experienced by breast cancer survivors (BCS) following treatment. The influence of genetics on CRF has been sparingly investigated. This article aims to explore the suggested impact of the catechol-O-methyltransferase (COMT) Val158Met genotypes on fatigue and to evaluate the effect on other potentially related patient-reported outcomes such as quality of life, diet, pain, or emotional facets; and also the effect on objective variables such as, heart rate variability (HRV), physical activity (PA), and biomarkers (cortisol, neutrophil-to-lymphocyte ratio, and noradrenaline).

Methods: A total of 79 BCS who had finished their treatment participated in this study. COMT genotypes were categorized as Val/Val, Val/Met, or Met/Met. PERFORM questionnaire was utilized to evaluate CRF. PA and HRV were objectively measured. The rest of the variables was assessed by questionnaires.

Results: BCS with Met/Met genotype reported higher levels of fatigue ($p = 0.031$), compared to those with Val/Met or Val/Val genotypes. No additional associations were found with other self-reported variables, HRV, PA, or the analysed biomarkers. The findings suggest that BCS with Met/Met genotype exhibit more elevated levels of fatigue.

Conclusion: Genetic factors could have a role in the pathogenesis of CRF. BCS with the Met/Met genotype may experience higher levels of CRF. Personalized interventions based on genetic profiling could help manage CRF more effectively.

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1. Introduction

Cancer-related fatigue (CRF) is characterized as a persistent and distressing subjective feeling of physical, emotional, and cognitive exhaustion linked to cancer and its treatment, not directly related to recent activity, disrupting normal functioning, and unalleviated by rest or sleep [1]. The prevalence of CRF can vary, often reaching 100% during cancer treatment [2], but approximately 25% of breast cancer survivors (BCS) experience long-lasting CRF that can persist for a decade or more after their initial diagnosis [3]. Reported rates, however, can be influenced by factors such as the type of cancer [4], sex [5], cancer stage [6], active treatments being administered [7], or the time elapsed since treatment completion [6]. Previous reviews have explored the underlying biological mechanisms of CRF in a general context [8–10]. However, BCS present unique characteristics including sex-related genetic and hormonal factors, as well as specific treatments involving cardiotoxic drugs and hormonal therapies. Besides that, CRF may be more common in BCS compared to survivors of other cancer types [4,11]. Thus, it is justified to investigate the biological mechanisms of CRF in this population of BCS post-treatment completion [12].

A recent scoping review has postulated that most of the studies in BCS evaluated inflammation as the main pathway driving fatigue, followed by HPA, and ANS dysfunction [13]. However, the evidence about inflammation is inconclusive. The authors suggested some potentially involved mechanisms insufficiently explored such as endocannabinoid system [14,15], mitochondrial dysfunction [16] and genomics. In this regard, the role of the catechol-O-methyltransferase (COMT) gene in BCS is not yet fully understood. This enzyme is involved in the metabolic breakdown of dopamine, norepinephrine, and epinephrine. The single-nucleotide polymorphism COMT Val158Met leads to the substitution of valine (Val) with methionine (Met) at codon 158 on chromosome 22q11 [17].

It is well-documented that genetic polymorphism resulting from a G to A nucleotide substitution at codon 158 of the COMT gene leads to a Val-to-Met amino acid change, causing variations in gene activity. The presence of the Val allele (Val/Val) results in a stable, highly active COMT variant, which exhibits approximately 3–4 times higher enzymatic activity compared to the Met allele (Val/Met, Met/Met) [18,19]. Reciprocally, the Met allele carriers have less stable and lower-activity variants [18]. Consequently, individuals with Val alleles experience more efficient degradation of dopamine, resulting in lower availability of this neurotransmitter at synaptic receptors. Val158 allele carriers, known as 'warriors,' in the literature about management of stress could have an advantage in processing aversive stimuli. On the contrary, individuals with Met158 alleles, known as 'worriers', would have a worse performance in conditions of stress [20].

Small and colleagues revealed that BCS with the Val allele showed poorer performance on attention, verbal fluency, and motor speed tests compared to those with the Met allele [21]. These findings imply that the cognitive health of BCS may be influenced by the distribution of the Val158Met polymorphism, underscoring the importance of this gene in clinical contexts. It is noteworthy that BCS patients grapple with various cancer-related symptoms, including fatigue, anxiety, pain, sleep disturbances, altered body image, and cognitive deficits [22]. Fatigue is the most prevalent and debilitating symptom in BCS. The prevalence of CRF has been described as reaching up to 40% among BCS [4]. In our original sample, we found that the prevalence of fatigue interfering with quality of

life was 43% [23]. Regarding biomarkers, cortisol, and neutrophil-to-lymphocyte ratio (NLR) were related to CRF. However, noradrenaline was not [24]. Functional limitations appear to be linked to fatigue, highlighting their significant impact on individuals' well-being [25]. Fernández-de-las-Peñas et al. [26] had previously revealed that genetic COMT variations could have a role in fatigue and pain reported by BCS. Therefore, the aims of this secondary post-hoc analysis were (1) to investigate the association of the Val158Met polymorphism with fatigue in BCS after the treatment; and (2) to explore the relevance of the Val158Met polymorphism in other outcomes potentially related such as quality of life, pain and emotional facets; (3) to assess interactions with potentially related biomarkers such as cortisol and norepinephrine and incidentally heart rate; (4) to look over physical activity (PA) as a behaviour potentially mediated by COMT, in order to check whether the Val/Val carriers were more active.

2. Methods

2.1. Participants

Patients were recruited through oncologists during the follow-up visits at Hospital Universitario Puerta de Hierro Majadahonda (Madrid, Spain). Inclusion criteria were to be aged 18 or older, diagnosed with localized breast cancer (stages I-III), have completed their treatments (trastuzumab and hormonal therapy were allowed during the evaluation), to be free from disease, and had signed the written informed consent form.

2.2. Study design

It is a descriptive and post hoc study with sample characteristics which have been previously described [23]. As a secondary objective, associations between CRF and different blood biomarkers have also been reported. This manuscript aims to identify potential relations between COMT genotypes and CRF, as well as to explore other variables of interest hypothetically related to COMT genotypes, namely pain, insomnia, emotional aspects, quality of life, heart rate, heart rate variability (HRV), and PA. The research protocol (PH-UEM-05) received approval from the relevant Ethics Committee and the study was conducted in accordance with the Declaration of Helsinki and pertinent European regulations.

2.3. Outcomes

Fatigue. CRF was evaluated using the PERFORM questionnaire, a validated and reliable 12-item scale designed specifically for cancer patients in clinical practice, as previously established [27]. The questionnaire has demonstrated its feasibility, validity, reliability, and sensitivity. The total score on the PERFORM questionnaire ranges from 12 to 60, with higher scores indicating lower levels of fatigue. In terms of reliability, the overall Cronbach's alpha coefficient was 0.9, and it displayed good convergent validity (0.8) and sensitivity to change (effect size 0.5–1). Notably, a clinically significant improvement required a minimum change of 3.5 points in the overall score, equivalent to a gain of 1 g/dl of

hemoglobin [28]. The threshold for considering fatigue as significant due to its impact on quality of life has been established at 45.8 in BCS [23].

Self-perceived health was assessed using a self-reported questionnaire.

Quality of life was measured by The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire EORTC QLQ-C30. This instrument encompasses five functional domains (physical, role, cognitive, emotional, and social functioning) as well as three symptom items (fatigue, pain, and nausea-vomiting). The raw scores are transformed linearly such that all scales range from 0 to 100. A higher score represents a higher level of functioning and for symptom scales a higher level of symptoms. Additionally, it includes a scale for global health status and overall QOL, along with several individual items to evaluate additional symptoms. The EORTC QLQ-C30 has undergone extensive validation, demonstrating favourable psychometric properties and cultural validity [29].

Heart rate was measured before (basal heart rate) and immediately after the tests with a heart rate telemeter, and the recovery heart rate was measured one minute after finishing.

Heart rate variability (HRV) refers to the fluctuations in the time intervals between successive heartbeats, serving as an indicator of the autonomic nervous system functioning. In general, higher variability is associated with better cardiovascular health and autonomic regulation. HRV was measured during two different stages with different ANS elicitation: 10 min lying down and 7 min standing up. The participant was instructed to avoid making movements and to remain as relaxed as possible. A Polar chest band connected to a watch (v800) was used. This device provides the instantaneous RR interval series, derived from the recorded ECG, with a resolution of 1 ms. The central interval of each stage has been considered, subdividing it into overlapping 3-minute windows in which HRV features are estimated and then averaged. Ectopic beats or false detections have been identified and corrected (only if corresponding gaps last less than 2 s, otherwise HRV analysis was not conducted), as proposed in [30]. Time domain HRV indices are calculated over the corrected RR series: standard deviation of normal RR intervals (SDNN), and square root of the mean of the squared differences between successive intervals (RMSSD).

Disease-related clinical data. This data was obtained by healthcare professionals from medical records.

Anthropometry. Body Mass Index (BMI) was calculated dividing body mass by the square of height (kg/m^2). All metrics, including waist and hip circumference, adhered to global guidelines during the measurements [31].

Blood biomarkers. Whole venous blood samples were collected after an overnight fast. Part of these samples was promptly used to assay cortisol (using the Advia Centaur XPT Immunoassay System). Neutrophils and lymphocytes were measured with an automated system (model XN-10 and XN-20, Sysmex; Kobe, Japan), and the neutrophil-to-lymphocyte ratio (NLR) was calculated. Noradrenaline (NA) was determined using a competitive inhibition enzyme immunoassay kit (EU2548, EU2565 Fine Test, Wuhan Fine Biotech Co., Ltd) following the manufacturer's instructions. The sensitivity for NA/NE was 9,375 pg/ml and range of detection was 15,625-1000 pg/ml. Prism software (GraphPad Software Inc., U.S.A.) was used for result analysis. These samples were processed following standard

operating procedures with the requisite approvals from the Ethics and Scientific Committees.

COMT genotypes. The genomic DNA of all the participants was analysed in order to study the Single Nucleotide Polymorfism rs4680 of COMT gene. TaqMan® SNP Genotyping Assay (Applied Biosystems™) was performed to assign the Val158/Val158, Val158/Met158 and Met158/Met158 COMT genotypes. We used a StepOnePlus™ Real-Time PCR System following the supplier's method.

2.4. Statistical analysis

Bivariate linear regressions were employed to assess the effects of COMT genotypes on fatigue scores (see Table 2). Dichotomous recodifications of COMT status were used to estimate their distinctive effect on each of the selected dependent variables. Specifically, two separate estimates were obtained for observations classified as Val/Val and Met/Met against the reference category Val/Met, which has the largest number of observations. This makes between group comparisons more reliable. Statistical significance was determined at a p-value threshold of <0.05. All data analyses were performed utilizing STATA v 17.1 (StataCorp, LLC; College Station, TX, U.S.A.) statistical software.

3. Results

3.1. Descriptive

A total of 79 BCS, with ages ranging from 34 to 69 years ($M = 51.1$, SD = 7.7), were enrolled in the study. Forty-six percent received both chemotherapy, and radiotherapy after surgery. The mean and standard deviation of time from diagnosis were 2.08, SD = 1.71 years. About half of patients of the sample would have clinically significant fatigue [23]. In terms of COMT genotypes, 23.5%, had the Val/Val genotype, 27.2% had the Met/Met genotype, and the remaining 49.4% had the Val/Met genotype. Descriptive data is detailed in Table 1.

Table 1. Descriptive data.

	Variables	Mean (SD) or percentage (%)
Anthropometry	Age (yrs)	51.1 (7.7)
	Weight (kg)	68.2 (11.6)
	Height (m)	1.6 (0.1)
	BMI (kg/m^2)	25.9 (4.6)
	Waist (cm)	84.9 (11.73)
	Hip (cm)	102.7 (9.32)
	WHI (waist/hip)	0.83 (0.07)
Clinical data	Stage I	39.7%
	Stage II	43.8%
	Stage III	16.4%
	Tumour Side (left)	54.1%
	Surgery (only)	14.9%
	Surgery & RT	12.2%
	Surgery & CT	27%
	Surgery, CT & RT	45.9%
	Time from diagnosis (months)	31.13 (20.39)

(*Continued*)

Table 1. Continued.

	Variables	Mean (SD) or percentage (%)
Health perceived	Very good	12.3%
	Good	57.5%
	Regular	27.4%
	Bad	2.7%
COMT genotypes	Val/Val	23.5%
	Met/Met	27.2%
	Val/Met	49.4%
Fatigue	PERFORM (0-60)	47.11 (11.83)
EORTC-QLQ30	Pain	22.64 (26.22)
	Insomnia	45.77 (35.22)
	Emotional	74.67 (26.78)
	Global	68.21 (20.67)
Biomarkers	Cortisol (µg/dL)	16.6 (6.4)
	NLR	2.1 (.9)
	Noradrenaline (pg/mL)	60.1 (55.0)
Heart rate variability	SDNN standing (ms)	31.33 (18.41)
	SDNN supine (ms)	31.38 (20.71)
	RMSS standing (ms)	14.44 (13.08)
	RMSS supine (ms)	22.08 (20.86)
Physical activity	MVPA (minutes)	314.7 (195.96)
	Sedentary time (minutes)	3761.5 (943.93)

BMI: Body mass index; CT: Chemotherapy; EORTC-QLQ30: EORTC-QLQ30 stands for European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire 30; NLR: Neutrophil-to-lymphocyte ratio; MVPA: Moderate to vigorous physical activity; RT: Radiotherapy; SDNN: Stands for Standard Deviation of Normal-to-Normal intervals; RMSS: Root Mean Square of Successive Differences;;WHI: Waist-to hip index.

COMT and fatigue associations: Fatigue was related to COMT genotypes. Specifically, Met/Met allele carriers, reported higher scores of fatigue ($p = 0.031$). Table 2 shows the linear regressions results. For the rest of the variables, no significant associations with COMT genotypes were found.

Table 2. Linear regressions results (ref. category Val/Met).

Variables	COMT	Coefficient	SE	$P > t$
Fatigue (PERFORM)	Val/Val	−4.93	3.47	0.161
	Met/Met	−8.057	3.64	0.031*
Pain	Val/Val	3.57	10.40	0.732
	Met/Met	8.78	10.40	0.402
Insomnia	Val/Val	−4.05	10.75	0.708
	Met/Met	4.29	10.76	0.692
Emotional	Val/Val	11.02	8.09	0.178
	Met/Met	3.21	8.09	0.693
Health perceived	Val/Val	0.071	0.20	0.72
	Met/Met	0.34	0.19	0.09
Global Quality of life	Val/Val	3.28	6.46	0.613
	Met/Met	−3.80	6.32	0.550
Cortisol	Val/Val	3.15	1.83	0.089
	Met/Met	0.83	1.76	0.638
NLR	Val/Val	-.24	.25	0.339
	Met/Met	.20	.25	.421
Noradrenaline	Val/Val	14.07	15.95	0.381
	Met/Met	8.06	15.95	0.615
Basal heart rate	Val/Val	4.30	3.58	0.234
	Met/Met	2.66	3.66	0.47

(*Continued*)

Table 2. Continued.

Variables	COMT	Coefficient	SE	$P > t$
Recovery heart rate	Val/Val	2.33	5.50	0.673
	Met/Met	1.39	5.50	0.801
HRV SDNN (standing)	Val/Val	−4.53	7.56	0.55
	Met/Met	−6.19	6.72	0.36
HRV SDNN (supine)	Val/Val	0.38	8.48	0.97
	Met/Met	−3.99	7.36	0.60
HRV RMSS (standing)	Val/Val	−3.03	5.30	0.571
	Met/Met	−6.41	4.72	0.18
HRV RMSS (supine)	Val/Val	5.15	8.54	0.550
	Met/Met	0.30	7.41	0.97
MVPA	Val/Val	−55.9	67.47	0.411
	Met/Met	−30.72	61.02	0.617
Sedentary time	Val/Val	−438.31	317.74	0.173
	Met/Met	96.46	287.40	0.738

MVPA: Moderate to vigorous physical activity; NLR: Neutrophil-to-lymphocyte ratio; SDNN: Stands for Standard Deviation of Normal-to-Normal intervals; RMSS: Root Mean Square of Successive Differences.

4. Discussion

This study suggests that BCS with Met/Met genotype would report higher levels of fatigue. No associations between COMT genotypes, self-reported pain, quality of life, emotional facets, diet, HRV or biomarkers were found in this sample. Upon identifying genomics as an unexplored area of research in CRF and having stored biological samples, we decided to launch the present study. Therefore, this is a post-hoc, non-interventional, non – initially planned study in which subtle differences were not expected to be detected. Specifically, pain has been described as one of the clustered symptoms for BCS who report CRF after treatment.

Previously, Met/Met genotype in patients with migraine [32] or fibromyalgia [33] had been associated with a more severe form of the disease compared with those with the Val/Val genotype. Differences in results might be explained by the single nucleotide polymorphism (SNP) rs4680 (Val158Met) that was studied in our sample which could not account alone for the observed variations in pain perception [34]. Interestingly, a systematic review studying rs4680 polymorphisms effects on pain, concluded inconsistent evidence with a small effect in fibromyalgia, headache, and chronic pain [32]. It is possible that multiple polymorphisms may interact at the same time and impact nociceptive pain mechanisms among BCS. It is also possible that the type and location of pain determine the sensitivity to polymorphisms [35,36].

Since this was an exploratory analysis, characteristics of pain were not properly investigated but, in any case, we evaluated self-reported pain due to health condition. Contrary to our results, Met/Met genotype has been associated to higher sensory and affective ratings of pain [37] and a more negative internal affective state in non-cancer population [38]. Previously Fernández-de-las-Peñas et al. [26] found that Met/Met carriers of COMT rs4680 polymorphisms reported greater intensity pain symptoms and higher pressure

pain hypersensitivity in BCS. It is worth noting that Yao, Zubieta and Fernandez de las Peñas, included in their studies an induced-pain model which could work differently from self-reported pain [26,37,38].

Intriguingly Met homozygotes have stronger activation of pain-related areas when investigating pain sensitivity without differences in self-reported pain [35]. Also, other SNPs in the COMT gene such as rs6269, rs4633, rs4818, do not lead to amino acid changes but to processes such as DNA transcription, RNA splicing, mRNA stability, transport and translation. Whereas Val158Met seems to play a role in the temporal summation of pain, other SNPs could have a role in resting nociceptive sensitivity. Future research in this field could encompass multiple polymorphisms and also a specific study of pain characteristics.

We were specially interested in the study of biomarkers, since they would be the immediate consequence of gene mutations of an enzyme which is involved in catecholamines and dopamine metabolism. However, we could not find any association with noradrenaline levels. No differences were either found in cortisol levels, although in this case there was a trend towards significance ($p = 0.089$) and could warrant further research. Previously, we found associations between lower cortisol levels and CRF in this population [39]. It has been reported that Met/Met carriers exposed to early life adversity could respond to stressful situations with smaller levels of cortisol [40]. Continuing research on cortisol as a biological mechanism of fatigue determined by COMT is worthwhile. We suggest future investigation about how cortisol could potentially act as a mediator between fatigue and COMT genotypes. Additionally, we explored the potential association with NLR ratio since it had also been associated with CRF in this sample [39] resulting negative as well.

We hypothesized that as a consequence of catecholamines metabolism disruption, HRV would be different in different carriers expecting to find a higher HRV among Val/Val carriers. It should be reminded that BHR was positively associated with CRF in this population [23]. Unexpectedly, we did not find any association with HRV values derived from the RR series provided by a validated device.

This study would give support to the previously suggested association between COMT and CRF in BCS [26]. However, some questions could arise regarding the type of statistical analysis and the lack of a parallel enzymatic activity gradient along the fatigue scores. The selection of ValMet as the reference group in this case, was driven by statistical considerations, particularly its position as the mode. Though theoretically the enzymatic activity gradient (MetMet < ValMet < ValVal) should parallel fatigue scores, we cannot observe that perfect slope because of the unfortunate lack of patients with high fatigue scores (45–55) within the Val/Val category despite ValVal category including the highest scores of the sample (55–60) (See Kernel Density Distribution as Appendix). This distributional discrepancy is related to the small number of BCS with ValVal genotype. We have retrospectively estimated that 36 cases per group would have been needed to detect differences.

Thus, our post-hoc analysis provides additional evidence endorsing the association between COMT and CRF, as previously demonstrated by Fernández-de-las-Peñas et al. These studies used different scales (Perform and Piper) but both are validated multidimensional questionnaires. Remarkably, we found that the absence of valine translated to a 17% increase within Perform and this result closely aligns with 16% increase in the

Piper fatigue scale in the work of Fernandez de las Peñas. It is our opinion that this is a noteworthy finding as establishing consistent results in this field is always remarkable [13]. Moreover, these results could pave the way for genetics in a field closely tied to psychosocial determinants such as fatigue. Acknowledging a predisposing condition to report CRF, would facilitate the understanding of treating physicians and would also eliminate some culpability from patients who suffer it and sometimes feel guilty for that. In this regard, CRF in BCS may reflect loss of adaptability of the neuroendocrine stress response in a subgroup of women. However, we still lack a comprehensive understanding of the pathway through which fatigue occurs. Further studies with larger samples are needed to explore the associations between these variables.

The findings of our study align with principles of personalized medicine [41], where genetic research facilitates the identification of patient groups that can benefit from targeted symptom intervention. Patients carrying a favourable genotype could obtain more benefit from any intervention and this information could be useful to stratify patients in randomized controlled trials [42]. Shifting the focus on groups experiencing more severe fatigue to provide specialized care is crucial. If genetics underlie patients' fatigue, perhaps new intervention approaches need to be devised for fatigue management rather than focus solely on its assessment. It might be interesting to divert attention away from individualism, which hinges on personal characteristics as determinants of fatigue, and instead explore the genetic aspects that could be influencing it. Future studies could include sociodemographic factors in their research to understand their interactions with fatigue and its genetic determinants.

Although the results of the present study are encouraging, a number of limitations should be recognized. We acknowledge that our study is a post-hoc analysis aimed at tentatively contributing to an emerging area of research. The sample was small and mainly composed of white BCS; therefore, extrapolation of current results to more diverse populations should be done cautiously. We recognize that our study was underpowered for detecting differences across allelic groups, specifically in Val/Val and Met/Met groups. And moreover we exclusively examined the Val158Met (rs4680) nucleotide polymorphism. Subsequent investigations should explore the impact of various Val158Met polymorphisms, with other genetic factors, on biological markers and CRF in BCS. Researchers have also proposed to study gene expression before and after treatment [43]. Lastly, we acknowledge that assessment of pain was not specific regarding type and location. It is crucial to assess whether the observed associations in our current study persist over time, considering that some BCS may be in the process of recovering from treatment side effects, and certain associations might be transient. Future research should explore COMT genotypes and CRF in other tumours and also in males.

5. Conclusions

These findings provide further evidence for pathophysiological mechanisms driving CRF. Our results suggest that genetic polymorphisms could impact on CRF in the BCS population. Specifically, polymorphisms of COMT participating in the metabolism of catecholamines and dopamine and consequently in the regulation of the sympathetic nervous system, stress sensitivity and responsivity. Further studies with larger sample sizes are recommended to improve the robustness and external validity of the results. Longitudinal

studies as well as studies in other tumours are warranted. A better understanding of biological pathways will help researchers and healthcare specialists to improve the treatment of this distressing condition. Patients and healthcare professionals dealing with CRF should be aware that there are biological mechanisms interrelated with genetic variation, environmental and socio-psychological factors, which determine its onset, maintenance and even aggravation of this condition.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [MRE, DGG, AAB, NG, RB, ER, CM, HCB, ARC]. The first draft of the manuscript was written by [MRE and ARC] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Prior presentation

The results of this research have been presented in part at the 2024 MASCC annual meeting, Lille, June 27-29th.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Ethics Committee at Hospital Puerta de Hierro Majadahonda, Madrid.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

All participants involved in this study have provided their consent to publish the findings derived from their data.

Data availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Notes on contributors

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