

## Research Article

# The Anger Felt by Cancer Patients. It Could Be An Unexpected Obstacle To The Treatment Path?

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## Abstract

Anger is one of the possible reactions to cancer. There are mutual influences between cancer and psychological status, with repercussions on the immune system. The aim of this study was to analyze differences in the experience, expression and control of anger by gender and to measure the relationship between anger, anxiety, depression, quality of life, and progression of the disease. We have conducted a cross-sectional study assessing 281 cancer patients, using the STAXI-2, HADS and a visual analogue scale to measure Quality of Life. Results: Females reported significantly higher State and Trait Anger scores and lower Anger Control Out scores than males. In the whole sample the anger subscale scores increased with levels of anxiety or depression. In males, high State, Trait and Expression Anger subscale scores resulted associated with low Quality of Life, among females, this relationship seems to be weak. No differences emerged on STAXI-2 scales and subscales between patients in progression of disease. Conclusions: Anxiety, depression and anger seem to be organized into a pattern of a general emotional reaction. Since immunotherapy is the anticancer treatment that increases the body's natural defenses to fight disease, a balanced immune system has become the main concern. In conclusion, clinicians could gain important insights about their patients by looking at the result of validated self-report patient questionnaires, to identify patients with inadequate expression of emotion or too high levels of emotional reaction in order to improve quality of care and response to treatment.

**Keywords:** anger scale, cancer management, depression assessment, immunological characteristics quality of life

## Introduction

Anger is an emotion that in these present times is making itself noticed in many contexts and in everyday life. It is the reaction to the frustration that people are experiencing due to the poor prospects of economic development, the lack of work, for young and old, etc. In oncology, clinicians are led to think that anger is the emotional reaction that characterizes the moments behind the diagnosis to then give way to emotional experiences of anxiety and then later depression. For a long time it was hypothesized that there could be a sequence of psychological reactions conditioned by the distance from the diagnosis. Today the experience and manifestations of anger must be studied in a more specific way, especially in light of the evidence that has shown a sex-specific differences in activity of emotion processing regions [1,2]. In medicine we know that sex hormones influence the onset and severity of various immuno-modulate disease [3,4], and the role of the psychological state on the disease and vice versa is known. Different diseases could be influenced by the psychological status and gender, just as diagnoses influence the psychological status of the patient, perhaps differently in the two sexes. If on the one hand the knowledge on prevalence of anxiety and depression is now consolidated [5], on the other, knowledge about the differences between the sexes in anger is still limited. Common sense leads us to think that the expression of

anger outward is more frequent among males, although Aghaei [6] has found very similar anger scores between males and females in a sample of cancer patients admitted to the hospital for surgery. There is a need to study in depth the complex relationships between sex, psychological distress and disease, especially today that the use of immunotherapy treatments makes the picture more complicated. Scientific literature has proposed to distinguish among different components of anger. There are differences between expressing or inhibiting anger, between controlling it by adopting relaxation methods or rather strategies to shift attention towards other stimuli. Studies that investigated the aspects of suppression, repression, or restraint of anger [7] found that the suppressed anger was associated with health risk factors and early mortality for all-cause, included cardiovascular and cancer mortality, in women [6,8]. The inhibition of negative emotions plays an important role in how cancer patients adjust to the disease [9,10]. Low levels of anger were associated with maladaptive coping strategies to cancer [3,4]. Differently other researchers have found that a reaction of anger expression may be an important factor in the fight against cancer [11]. However, patients with high levels of intensity of anger should be evaluated carefully to determine whether the risk of acting out their anger represents a potential danger to themselves and others. Differently, moderate anger experiences may guide problem-solving behaviour and people may be more assertive than aggressive.

Anyways anger is a human emotion that can vary in component, intensity, expression and control [12] and each pattern can have different meaning and relationship with other emotional feeling and behavioural experiences for people. To study the multifaceted construct of anger the State-Trait Anger Expression Inventory-2TM [13,14] has been developed and validated. The questionnaire has been developed to recognize 11 components of experience, expression and control of anger. The State Anger refers to the intensity of the individual's angry feelings at a specified time or at the time of testing. The State Anger splits into 3 domains: Feeling Angry, to Feel like Expressing Anger Verbally and Feel like Expressing Anger Physically. The first is related with annoyance, irritation, anger or fury. The second, with the desire to express anger by swearing, cursing, yelling or screaming. The third, reflects the inclination to hit someone or to break things. Trait anger measures a predisposition to become angry and is critical for understanding how often a person becomes angry. Anger experienced quickly and with little provocation reflects an Angry Temperament, as a predisposition, while the tendency to become angry when people receives negative feedback is Angry Reaction. Anger Expression Out and Anger Expression In describe the extent to which people expresses emotional experiences of anger in an outwardly negative and poorly controlled way or vice versa to be under-reactive, suppressing, repressing, or denying anger feelings because uncomfortable. Anger Control Out involves the expenditure of energy to monitor and control the expression of angry. People with high Anger Control Out may not be in touch with their emotions and may not recognize the need to act on solving the problem causing the anger. Last, Anger Control In reflects how a person attempts to relax and reduce angry before got out of control. The aim of this study was to measure the sexes differences among cancer patients related to: (1) experience, expression and control of anger; (2) relationship between anger components and anxiety, depression, quality of life, and progression of disease.

## Materials and Methods

142 male cancer patients (mean age= 65.19; standard deviation, SD = 12.53) and 139 female cancer patients (mean age = 62.57; SD = 11.47) admitted for oncological treatment at the Day Hospital were consecutively enrolled in this study. Informed consent was obtained for all patients at the enrolment in the study. The Committee of Ethics of the hospital approved the study protocol (Prot. n. 39/CE/2017, 04 Oct 2017).

## Questionnaires

**State-Trait Anger Expression Inventory-2TM (STAXI-2)** [13,14]. The 57-item STAXI-2 consists of six main scales (State Anger, Trait Anger, Anger Expression Out, Anger Expression In, Anger Control Out and Anger Control In) and five subscales (for State Anger: Feeling Angry, to Feel like Expressing Anger Verbally and Feel like Expressing Anger Physically; for Trait Anger: Angry Temperament and Angry Reaction) to measure experience, expression and control of anger. The State Anger scale assesses the intensity of anger as an emotional state at a data time. The Trait Anger scale measures how often angry feelings are experienced over time. The Anger Expression Out and

Anger Expression In, Anger Control Out and Anger Control In scales assess four independent anger-related traits: expression of anger toward other persons or objects in the environment; holding in or suppressing angry feelings; controlling angry feelings by preventing the expression of anger toward other persons or objects in the environment; controlling suppressed angry feelings by calming down or cooling off, respectively. Each item has 4 options and the subjects graded themselves by using a 4-point Likert scale (from 1=almost never to 4=usually). In this study, internal consistency was good to excellent for all STAXI-2 scales, with Cronbach's alpha coefficients ranging from 0.69 (Anger Expression Out) to 0.93 (State Anger) for males, and from 0.72 (Anger Expression Out) to 0.93 (State Anger) for females.

**Hospital Anxiety and Depression Scale (HADS)** [15]. The HADS is a 14-item screening instrument for anxiety (7 items) and depression (7 items) in a non-psychiatric setting. Each item is scored from 0 (not present) to 3 (highly present). Separately for each scale (range 0-21), scores <8 suggest absence of disease, scores from 8 to 10 are considered borderline, and those >10 identify probable cases of anxiety or depression [16]. In this study, Cronbach's alpha coefficients were 0.78 and 0.79 for males and 0.82 and 0.75 for females, respectively for anxiety and depression.

**Quality of life (QoL) and perception of severity and curability of the disease** [17] were self- assessed by the patients using a 10-point rating scale (bad/excellent quality of life, very/not very severe, difficult/very easy to cure). Sociodemographic data and clinical information were also collected.

## Statistical Analyses

For descriptive purpose we divided patients into two categories according to differences in education (<=13yrs of school versus >13yrs). Marital status was dichotomized into persons living alone (single, divorced, widowed) and into those cohabiting (married, cohabiting). Data about presence of metastasis, lymphectomy, and progression of disease were also dichotomized (absent versus present). Cancer type with less than 5 patients were grouped together and labeled "other". For sub-analyses purpose, data about HADS anxiety and depression were divided into three groups (no disease, score 0-7; borderline, score 8-10, cases 11-21). All the raw questionnaire and 10-point rating scale scores were linearly transformed to 0-100 scales to allow comparability, using the

### Formula:

$$Tscore = (X - Xmin) / Xrange * n$$

where Tscore is the adjusted variable, X is the original variable, Xmin is the minimum observed value on the original variable and Xrange is the difference between the maximum potential score and the minimum potential score on the original variable and n is the upper limit of the rescaled variable. The Tcores are characterized by a distribution with a mean of 50 and a standard deviation (SD) of 10, with 0 and 100 assigned to the lowest and highest possible values, respectively. Continuous variables were reported as medians (and interquartile ranges [IQRs]) and as means (and SD or 95% Confidence

Intervals, 95% CIs), and inferences were tested with parametric or non-parametric tests accordingly with their distribution. Even if the sample distribution of the values was asymmetric, the data were also presented as means to allow better visualization of the results, since the median often coincided with the quartiles. Categorical variables were reported as proportions and chi-squared or Fisher's exact test were used for comparison. Cronbach's alpha was adopted to evaluate internal consistency of questionnaires scales and subscales. The analyzes were conducted separately from gender. All statistical analyses have been performed using STATA, version 11.0 (StataCorp, College Station, Tex).

## Results

A total of 281 cancer patients, 142 males and 139 females, aged

from 31 to 88 years, were enrolled in the study. Sociodemographic and clinical features are reported in Table 1, separately for gender. Males were older at diagnosis ( $p=0.016$ ), they had more frequently metastasis ( $p<0.001$ ) and an advanced cancer stadium ( $p<0.001$ ), a shorter length of disease ( $p=0.038$ ) and less chemotherapeutic treatments ( $p=0.001$ ), compared to females. In Table 2 mean values and 95% CIs of STAXI-2 and HADS domains, perception of qol, severity and curability of the disease are shown separately for males and females. Males reported lower mean scores in State ( $p=0.019$ ) and Trait Anger ( $p=0.030$ ), and higher mean scores in Anger Control In, than females. No differences emerged in Anger Expression, Out and In, and in Anger Control In between gender.

**Table 1:** Sociodemographic and clinical characteristics of the sample, separately for gender.

		males (N=142; 50,53%)		females (N=139; 49,47%)		pvalue*
		N	%	N	%	
<b>age, years (mean; 95%CI)</b>		65,19	63,11-67,27	62,57	60,65-64,49	0,069
<b>education</b>	≤13yrs	113	79,58	105	75,54	0,417
	>13yrs	29	20,42	34	24,46	
<b>married</b>	no	19	13,48	28	20,59	0,115
	yes	122	86,52	108	79,41	
<b>age at diagnosis (mean; 95%CI)</b>		63,13	60,96-65,30	59,43	57,34-61,52	<b>0,016</b>
<b>length of disease, years</b>		2,06	1,41-2,70	3,17	2,33-4,00	<b>0,038</b>
	0-1yrs	98	69,01	79	56,83	
	2-8 yrs	34	23,94	41	29,50	
	9+ yrs	10	7,04	19	13,67	
<b>cancer type</b>	colon	37	26,06	22	15,83	<b>&lt;0,001</b>
	melanoma	26	18,31	24	17,27	
	lung	34	23,94	14	10,07	
	breast	0	0,00	46	33,09	
	vescica	10	7,04	3	2,16	
	ovaio	0	0,00	12	8,63	
	gastrico	7	4,93	3	2,16	
	other	28	19,72	15	10,79	
<b>cancer stadium</b>	I	4	2,92	6	4,65	<b>&lt;0,001</b>
	II	2	1,46	22	17,05	
	III	26	18,98	23	17,83	
	IV	105	76,64	78	60,47	
<b>linfektomia</b>	no	67	47,18	33	23,74	<b>&lt;0,001</b>
	yes	68	47,89	101	72,66	
	missing value	7	4,93	5	3,60	
<b>metastasis at diagnosis</b>	no	72	50,70	104	74,82	<b>&lt;0,001</b>
	yes	69	48,59	35	25,18	
	missing value	1	0,70	0	0,00	
<b>radiotherapy</b>	no	111	78,17	91	65,47	<b>&lt;0,001</b>
	adjuvant	5	3,52	33	23,74	
	palliative	24	16,90	14	10,07	
	esclusiva	2	1,41	1	0,72	
<b>CHT</b>	no	103	72,54	63	45,32	<b>&lt;0,001</b>
	neoadjuvant	4	2,82	3	2,16	
	adjuvant	35	24,65	73	52,52	
<b>pre-CHT line (mean; 95%CI)</b>		2,30	1,70-2,91	4,03	3,33-4,72	<b>&lt;0,001</b>
<b>progression of disease</b>	no	28	19,72	45	32,37	<b>0,016</b>
	yes	114	80,28	94	67,63	
<b>* Chi2 test; Student t test</b>						

**Table 2:** Descriptive statistics for STAXI-2 scales, HADS scales, patient perception of quality of life (QOL), cancer severity and curability.

		males		females		
		(N=142; 50,53%)		(N=139; 49,47%)		
		mean	95%CI	mean	95%CI	p-value*
<b>STAXI</b>						
<b>Anger state</b>		7,84	5,47-10,21	11,45	8,71-14,18	<b>0,019</b>
	feeling angry	12,35	9,46-15,24	17,55	13,99-21,12	<b>0,040</b>
	verbal anger	7,56	4,50-10,62	12,09	8,46-15,72	<b>0,023</b>
	physical anger	3,62	1,56-5,67	4,70	2,61-6,69	0,472
<b>Anger trait</b>		24,88	21,50-28,27	29,34	25,93-32,74	<b>0,030</b>
	temperament	19,07	15,59-22,56	25,00	21,61-28,39	<b>0,002</b>
	reaction	31,87	27,70-36,04	35,13	31,05-39,21	0,145
<b>Anger expression</b>						
	out	23,88	21,26-26,51	24,85	22,16-27,54	0,566
	in	34,33	31,12-37,54	33,69	30,10-37,29	0,577
<b>Anger control</b>						
	out	66,33	62,15-70,51	60,19	55,96-64,43	<b>0,036</b>
	in	58,51	54,56-62,46	57,27	53,23-61,28	0,723
<b>HADS</b>						
	anxiety	26,89	24,02-29,77	35,46	32,28-38,63	<b>&lt;0,001</b>
	depression	27,20	24,16-30,23	31,41	28,35-34,48	<b>0,054</b>
<b>QOL</b>		6,81	6,45-7,17	6,40	6,03-6,78	0,091
<b>Cancer severity perception</b>		5,13	4,70-5,56	4,96	4,53-5,38	0,539
<b>Cancer curability perception</b>		6,38	5,99-6,78	6,20	5,79-6,62	0,517
* Kruskal-wallis test						

Males also reported lower mean score in HADS-Anxiety ( $p < 0.001$ ) and Depression scale ( $p = 0.054$ ). No significant differences emerged in perception of QoL, severity and curability of cancer between gender. Sixteen males (11.27%) and 32 females (23.02%) resulted probably-cases of anxiety (HADS- Anxiety score  $> 10$ ); anxiety was absent (score  $< 8$ ) in 76.76% of males and 56.12% of females, and borderline (scores between 8 and 10) in 11.97% of males and 20.86% of females. Eighteen males (12.68%) and 17 females (12.23%) resulted probably-cases of depression (HADS-Depression score  $> 10$ ); depression was absent (score  $< 8$ ) in 70.42% of males and 64.75% of females, and borderline (scores between 8 and 10) in 16.90% of males and 23.02% of females. STAXI-2 scale and subscale descriptive statistics, separately for categories of HADS-anxiety (absent, borderline, cases) and gender are shown in Table 3. Independently of gender, the anger subscale scores increased with levels of anxiety, excepted for both the Anger Control subscales with the exception for males for which the Anger Control Out scores decreased from absence to cases of anxiety. A similar pattern of associations (shown in Table 4) emerged respect to categories of HADS-depression (absent, borderline, cases). No relationship has been found between levels of Depression and Anger Control Out. The higher anger scores resulted in Anger Control In, Reaction and Anger Expression In compared to the other STAXI-2 subscale scores. STAXI-2 scale and subscale descriptive statistics,

separately for Quality of Life levels (low, medium, high) and gender are shown in Table 5. For males, a low QoL score was associated with high anger subscale scores, excepted for Anger Control subscales (high scores are associated with high QoL). Among females, the relationship between anger and QoL seems to be weak, excepted for the Anger Control subscales, which elevated scores are associated with good QoL. No differences emerged between STAXI-2 scales and subscales and progression of disease (PD) among females. Males in PD feel annoyance, irritation, anger or fury ( $p = 0.051$ ). The predisposition to become angry is not different between those with PD and no-PD. Differently, anger experienced quickly and with little provocation was higher among patients with PD than no-PD (see Table 6).

### Discussion

Among patients with a diagnosis of cancer, anger is one of the “expected” emotional reactions. Surprisingly we failed to found relationships between the characteristics of anger, its expression and control, and the clinical objective characteristics of the cancer as type, stadium, progression of disease, years from diagnosis, and being in chemotherapeutic treatment. Neither association have been found with patients’ sociodemographic characteristics, with the exclusion of years of education. To have less than 14 years of school is associated with high scores in State and Trait Anger, while having more than 13

**Table 3:** Descriptive statistics of STAXI-2 scales and subscales, separately for categories of HADS-Anxiety and Gender

HADS-Anxiety		absent (<=7)		borderline (8-10)		cases (>=11)		
<b>Males, N=142</b>		N=109			N=17	N=16		pvalue
<b>Anger, state</b>	mean, SD	4,38	8,07	10,59	13,30	28,47	26,66	
	median, IQR	0,00	0-4,44	6,67	4,44-13,33	17,78	6,67-53,33	<0,001
feeling	mean, SD	7,77	11,95	18,82	14,76	36,67	27,65	
	median, IQR	0,00	0-13,33	20,00	13,33-26,67	30,00	13,33-63,33	<0,001
verbal anger	mean, SD	3,79	10,48	8,63	22,58	32,08	33,40	
	median, IQR	0,00	0-0	0,00	0-6,67	16,67	3,33-60	<0,001
physical anger	mean, SD	1,59	5,73	4,31	14,52	16,67	27,76	

	median, IQR	0,00	0-0	0,00	0-6,67	0,00	0-23,33	0,002
<b>Anger, trait</b>	mean, SD	21,37	17,80	33,33	25,32	39,81	23,17	
	median, IQR	14,81	7,41-29,63	25,93	14,81-44,44	38,89	20,37-53,70	0,002
temperament	mean, SD	15,60	18,95	29,90	25,01	31,25	22,87	
	median, IQR	8,33	0-25	25,00	8,33-50	33,33	8,33-41,67	0,002
reaction	mean, SD	28,44	22,60	38,24	29,76	48,44	29,85	
	median, IQR	25,00	8,33-41,67	25,00	25-33,33	37,50	29,17-79,17	0,017
<b>Expression Out</b>	mean, SD	22,13	14,86	25,74	16,35	33,85	18,81	
	median, IQR	20,83	8,33-33,33	25,00	12,5-33,33	31,25	22,92-43,75	0,038
<b>Expression IN</b>	mean, SD	31,15	18,73	42,89	17,85	46,88	18,35	
	median, IQR	29,17	16,67-41,67	45,83	29,17-54,17	45,83	35,42-62,5	0,001
<b>Control Out</b>	mean, SD	69,46	24,68	60,50	19,47	51,19	28,70	
	median, IQR	76,19	57,14-90,48	57,14	42,86-71,43	50,00	30,95-73,81	0,016
<b>Control In</b>	mean, SD	59,82	24,03	58,82	17,61	49,22	26,93	
	median, IQR	62,50	45,83-79,17	54,17	50-66,67	43,75	33,33-72,92	0,289

HADS-Anxiety		absent (<=7)		borderline (8-10)		cases (>=11)		
<b>Females, N=139</b>		N=78		N=29		N=32		pvalue
<b>Anger, state</b>	mean, SD	5,36	8,55	11,57	15,53	25,56	22,01	
	median, IQR	2,22	0-6,67	4,44	2,22-20	18,89	8,89-43,33	<0,001
feeling	mean, SD	9,40	14,71	16,78	15,80	36,25	25,34	
	median, IQR	6,67	0-13,33	13,33	6,67-20	36,67	10-56,67	<0,001
verbal anger	mean, SD	5,56	12,73	12,41	21,58	27,71	30,06	
	median, IQR	0,00	0-6,67	0,00	0-20	20,00	0-46,67	<0,001
physical anger	mean, SD	1,11	3,47	5,52	14,04	12,71	19,63	
	median, IQR	0,00	0-0	0,00	0-0	0,00	0-20	<0,001
<b>Anger, trait</b>	mean, SD	22,27	16,16	32,57	23,31	43,63	18,69	
	median, IQR	18,52	11,11-33,33	29,63	14,81-48,15	44,44	29,63-55,55	<0,001
temperament	mean, SD	17,95	15,90	28,16	20,94	39,32	21,30	
	median, IQR	16,67	8,33-25	25,00	8,33-41,67	33,33	25-54,17	<0,001
reaction	mean, SD	27,99	21,36	38,51	27,59	47,48	21,58	
	median, IQR	25,00	8,33-41,67	33,33	16,67-58,33	50,00	33,33-62,5	<0,001
<b>Expression Out</b>	mean, SD	21,63	14,50	25,86	14,23	31,77	19,10	
	median, IQR	20,83	12,5-29,17	25,00	16,67-37,5	27,08	20,83-39,58	0,016
<b>Expression In</b>	mean, SD	28,79	19,83	30,89	16,20	48,18	23,45	
	median, IQR	25,00	12,5-45,83	29,17	20,83-41,67	47,92	29,17-60,42	<0,001
<b>Control Out</b>	mean, SD	62,82	25,87	55,67	23,64	57,89	25,11	
* Kruskal-wallis test	median, IQR	66,67	42,86-85,71	52,38	38,09-76,19	57,14	40,48-80,95	0,280
<b>Control In</b>	mean, SD	59,56	24,82	52,30	21,20	56,12	24,20	
	median, IQR	62,50	41,67-75	54,17	37,5-66,67	62,50	33,33-75	0,211

**Table 4:** Descriptive statistics of STAXI-2 scales and subscales, separately for categories of HADS-Depression and gender

HADS,Depression		absent (<=7)		borderline (8-10)		cases (>=11)		
Males, N=142		N=100		N=24		N=18		p-value
<b>Anger, state</b>	mean, SD	4,09	8,10	15,28	21,48	18,77	19,97	
	median, IQR	0,00	0-4,44	6,67	3,33-18,89	10,00	6,67-31,11	<0,001
feeling	mean, SD	6,60	9,11	23,61	23,91	29,60	24,21	
	median, IQR	0,00	0-13,33	20,00	6,67-30,00	23,33	13,33-40	<0,001
verbal anger	mean, SD	3,93	12,72	14,17	26,25	18,89	25,90	
	median, IQR	0,00	0-0,00	0,00	0-13,33	6,67	0-33,33	<0,001
physical anger	mean, SD	1,73	7,62	8,06	19,75	8,15	18,37	
	median, IQR	0,00	0-0,00	0,00	0-6,67	0,00	0-6,67	0,006
<b>Anger, trait</b>	mean, SD	21,19	18,52	31,64	18,85	36,42	26,17	
	median, IQR	14,81	7,41-29,63	29,63	22,22-50,00	24,07	18,52-62,96	0,003
temperament	mean, SD	15,25	19,21	27,78	21,80	28,70	24,12	
	median, IQR	8,33	0-25,00	33,33	4,17-41,67	20,83	8,33-50,00	0,003
reaction	mean, SD	28,33	23,21	36,46	25,63	45,37	30,28	
	median, IQR	25,00	8,33-33,33	33,33	12,5-54,17	37,50	25-83,33	0,024
<b>Expression Out</b>	mean, SD	21,88	14,57	28,65	16,95	28,70	19,43	
	median, IQR	20,83	8,33-31,25	27,08	16,67-41,67	27,08	16,67-41,67	0,105
<b>Expression IN</b>	mean, SD	30,83	19,27	41,32	17,55	44,44	16,85	
	median, IQR	27,08	16,67-41,67	41,67	29,17-54,17	45,83	33,33-54,17	0,002
<b>Control Out</b>	mean, SD	70,90	24,48	59,92	20,30	49,47	27,14	
	median, IQR	76,19	57,14-90,48	59,52	42,86-76,19	45,24	33,33-71,43	0,001
<b>Control In</b>	mean, SD	62,33	23,42	52,78	21,02	44,91	23,94	
	median, IQR	66,67	47,92-79,17	54,17	43,75-66,67	43,75	29,17-58,33	0,004

HADS,Depression		absent (<=7)		borderline (8-10)		cases (>=11)		
Females, N=139		N=90		N=32		N=17		p-value
<b>Anger, state</b>	mean, SD	7,41	12,64	17,78	20,59	19,74	18,34	
	median, IQR	2,22	0-8,89	13,33	0-22,22	17,78	2,22-24,44	<0,001
feeling	mean, SD	12,22	17,20	23,75	23,34	30,59	25,06	
	median, IQR	6,67	0-13,33	20,00	0-43,33	33,33	6,67-53,33	0,002
verbal anger	mean, SD	7,48	17,04	19,58	27,09	22,35	25,71	
	median, IQR	0,00	0-6,67	10,00	0-26,67	13,33	0-33,33	0,001
physical anger	mean, SD	2,52	8,75	10,00	17,92	6,27	14,43	
	median, IQR	0,00	0-0,00	0,00	0-16,67	0,00	0-0,00	0,038
<b>Anger, trait</b>	mean, SD	26,01	18,61	31,60	23,48	42,70	17,23	
	median, IQR	22,22	11,11-37,04	29,62	12,96-44,44	40,74	33,33-55,56	0,004
temperament	mean, SD	21,85	17,47	26,56	23,99	38,72	21,44	
	median, IQR	16,67	8,33-33,33	25,00	8,33-41,67	33,33	25-58,33	0,012
reaction	mean, SD	31,57	23,62	37,05	25,49	49,51	21,14	
	median, IQR	25,00	8,33-50,00	33,33	16,67-58,33	50,00	33,33-66,67	0,013
<b>Expression Out</b>	mean, SD	22,96	14,54	26,95	17,13	30,88	20,20	
	median, IQR	20,83	12,5-33,33	22,92	14,58-37,50	25,00	20,83-37,50	0,227
<b>Expression In</b>	mean, SD	30,60	20,68	32,29	16,93	52,70	24,24	
	median, IQR	25,00	16,67-45,83	31,25	20,83-41,67	50,00	33,33-66,67	0,003
<b>Control Out</b>	mean, SD	63,76	23,89	52,83	26,43	55,18	27,72	
	median, IQR	66,67	47,92-80,95	50,00	33,33-76,19	61,94	38,10-76,19	0,083
<b>Control In</b>	mean, SD	60,93	23,50	50,39	23,00	50,74	25,44	
	median, IQR	64,58	45,83-75,00	45,83	35,42-66,67	54,17	29,17-75,00	0,029

\* Kruskal-wallis test

**Table 5:** Descriptive statistics of STAXI-2 scales and subscales, separately for Quality of Life and gender

Quality of Life		low (1-3)		medium (4-7)		high (8-10)		pvalue
Males, N=142		N=100		N=24		N=18		
<b>Anger, state</b>	mean, SD	21,11	24,72	8,01	13,27	5,09	11,21	
	median, IQR	7,78	2,22-41,11	4,44	0-8,89	0,00	0-4,44	<b>0,002</b>
feeling	mean, SD	30,56	30,01	13,73	16,53	7,31	12,11	
	median, IQR	16,67	6,67-56,67	6,67	0-20,00	0,00	0-13,33	<b>0,001</b>
verbal anger	mean, SD	25,00	33,77	6,27	14,66	5,59	16,69	
	median, IQR	6,67	0-50,00	0,00	0-6,67	0,00	0-0,00	<b>0,017</b>
physical anger	mean, SD	7,78	14,17	4,02	13,97	2,37	9,96	
	median, IQR	0,00	0-10,00	0,00	0-0,00	0,00	0-0,00	<b>0,040</b>
<b>Anger, trait</b>	mean, SD	41,36	23,79	26,31	20,99	20,13	17,22	
	median, IQR	44,44	24,07-55,56	20,37	11,11-37,04	14,81	7,41-25,93	<b>0,006</b>
temperament	mean, SD	34,72	22,43	20,96	21,57	13,98	18,47	
	median, IQR	33,33	12,5-54,17	16,67	0-33,33	8,33	0-25,00	<b>0,004</b>
reaction	mean, SD	46,53	27,40	33,46	26,33	27,28	22,29	
	median, IQR	41,67	29,17-62,50	25,00	16,67-45,83	25,00	8,33-33-33	<b>0,032</b>
<b>Expression Out</b>	mean, SD	31,60	22,29	24,94	14,32	21,24	15,68	
	median, IQR	29,17	14,58-39,58	20,83	14,58-33,33	16,67	8,33-29,17	0,131
<b>Expression IN</b>	mean, SD	38,54	19,15	39,52	18,37	27,82	18,81	
	median, IQR	35,42	29,17-47,92	41,67	25-52,08	25,00	8,33-41,67	<b>0,001</b>
<b>Control Out</b>	mean, SD	40,87	19,63	70,03	22,77	67,20	26,17	
	median, IQR	38,10	28,57-52,38	73,81	52,38-90,48	71,43	52,38-85,71	<b>0,001</b>
<b>Control In</b>	mean, SD	36,46	15,19	60,23	21,48	60,89	25,59	
	median, IQR	41,67	29,17-45,83	60,42	45,83-77,08	66,67	45,83-79,17	<b>0,001</b>

Quality of Life		low (1-3)		medium (4-7)		high (8-10)		pvalue
Females, N=139		N=12		N=77		N=50		
<b>Anger, state</b>	mean, SD	12,41	10,05	13,33	17,38	7,91	15,44	
	median, IQR	15,56	2,22-17,78	6,67	2,22-20,00	2,22	0-6,67	<b>0,008</b>
feeling	mean, SD	25,56	20,66	19,05	20,34	12,13	20,90	
	median, IQR	20	6,67-46,67	13,33	0-26,67	6,67	0-13,33	<b>0,006</b>
verbal anger	mean, SD	8,89	11,84	15,57	24,49	7,33	17,68	
	median, IQR	0	0-20,00	0	0-20,00	0,00	0-0,00	<b>0,023</b>
physical anger	mean, SD	2,78	6,64	5,28	13,86	4,27	11,33	
	median, IQR	0	0-0,00	0	0-0,00	0,00	0-0,00	0,868
<b>Anger, trait</b>	mean, SD	34,26	23,64	32,28	21,62	23,63	16,05	
	median, IQR	27,78	16,67-55,56	29,63	14,81-44,44	22,22	11,11-33,33	0,078
temperament	mean, SD	31,94	25,08	27,16	21,90	20,00	14,96	
	median, IQR	25	16,67-50,00	25	8,33-41,67	16,67	8,33-33,33	0,194
reaction	mean, SD	36,81	29,4	38,53	25,22	29,50	20,91	
	median, IQR	29,17	16,67-52,08	33,33	16,67-58,33	25,00	16,67-50,00	0,181
<b>Expression Out</b>	mean, SD	26,74	24,58	25,38	14,77	23,58	15,76	
	median, IQR	18,75	10,42-35,42	25	12,5-33,33	20,83	12,5-33,33	0,618
<b>Expression IN</b>	mean, SD	30,9	21,35	37,12	19,78	29,08	23,34	
	median, IQR	27,08	18,75-37,50	33,33	20,83-50,00	25,00	12,5-41,67	<b>0,037</b>
<b>Control Out</b>	mean, SD	44,84	28,31	62,77	23,62	59,90	26,14	
	median, IQR	42,86	28,57-64,29	66,67	42,86-80,95	61,90	38,09-80,95	0,102
<b>Control In</b>	mean, SD	37,15	23,13	59,63	22,76	58,42	24,22	
	median, IQR	33,33	18,75-52,08	62,50	41,67-75,00	62,50	41,67-75,00	<b>0,017</b>

\* Kruskal-wallis test

**Table 6:** Descriptive statistics of STAXI-2 scales and subscales by progression of disease and gender

Progression of disease			No		Yes	
<b>Males, N=142</b>			N=28		N=114	p-value
<b>Anger, state</b>	mean, SD	4,21	7,61	8,73	15,38	
	median, IQR	0,00	0-5,56	4,44	0-8,89	<b>0,079</b>
feeling	mean, SD	7,14	11,61	13,63	18,40	
	median, IQR	0,00	0-13,33	6,67	0-20,00	<b>0,051</b>
verbal anger	mean, SD	5,00	12,65	8,19	19,59	
	median, IQR	0,00	0-0,00	0,00	0-6,67	0,382
physical anger	mean, SD	0,48	1,75	4,39	13,71	
	median, IQR	0,00	0-0,00	0,00	0-0,00	0,125
<b>Anger, trait</b>	mean, SD	20,11	19,74	26,06	20,46	
	median, IQR	14,81	5,56-25,93	22,22	11,11-37,04	0,120
temperament	mean, SD	12,80	20,22	20,61	21,01	
	median, IQR	8,33	0-12,50	16,67	0-33,33	0,032
reaction	mean, SD	27,68	22,46	32,89	25,74	
	median, IQR	25,00	8,33-33,33	25,00	16,67-41,67	0,442
<b>Expression Out</b>	mean, SD	23,21	14,80	24,05	16,15	
	median, IQR	20,83	12,5-33,33	22,92	12,5-33,33	0,918
<b>Expression IN</b>	mean, SD	33,18	20,27	34,61	19,23	
	median, IQR	31,25	18,75-45,83	33,33	20,83-45,83	0,721
<b>Control Out</b>	mean, SD	73,13	19,58	64,66	26,20	
	median, IQR	73,81	59,52-90,48	71,43	42,86-85,71	0,183
<b>Control In</b>	mean, SD	65,33	20,26	56,83	24,37	
	median, IQR	64,58	52,08-83,33	58,33	41,67-75,00	0,113

Progression of disease		No		Yes		
<b>Females, N=139</b>		N=45		N=94		p-value
<b>Anger, state</b>	mean, SD	9,98	12,69	11,94	17,80	
	median, IQR	6,67	2,22-13,33	2,22	0-17,78	0,530
feeling	mean, SD	18,07	19,63	16,67	21,48	
	median, IQR	13,33	6,67-20,00	6,67	0-26,67	0,271
verbal anger	mean, SD	8,44	16,66	13,83	23,55	
	median, IQR	0,00	0-13,33	0,00	0-20,00	0,261
physical anger	mean, SD	3,41	9,06	5,32	13,81	
	median, IQR	0,00	0-0,00	0,00	0-0,00	0,984
<b>Anger, trait</b>	mean, SD	29,79	14,71	29,12	22,56	
	median, IQR	29,63	18,52-40,74	22,22	11,11-44,44	0,362
temperament	mean, SD	23,33	15,65	25,80	22,13	
	median, IQR	25,00	8,33-33,33	25,00	8,33-33,33	0,875
reaction	mean, SD	37,41	19,75	34,04	26,29	
	median, IQR	33,33	25-50,00	29,17	8,33-58,33	0,227
<b>Expression Out</b>	mean, SD	24,81	12,96	24,87	17,40	
	median, IQR	20,83	16,67-33,33	20,83	12,5-33,33	0,567
<b>Expression IN</b>	mean, SD	33,89	18,65	33,60	22,76	
	median, IQR	33,33	20,83-45,83	29,17	16,67-50,00	0,650
<b>Control Out</b>	mean, SD	60,11	23,31	60,23	26,26	
	median, IQR	61,90	42,86-76,19	61,90	42,86-80,95	0,869
<b>Control In</b>	mean, SD	57,41	22,27	57,18	24,87	
	median, IQR	62,50	41,67-75,00	62,50	41,67-75,00	0,941

\* Kruskal-wallis test



years of school is associated with more Anger Control In, males and females attempted to relax them to reduce angry. In this sample we have found low scores related to the intensity of the individual's angry feelings (Anger State), especially among males, and more high scores in the tendency to become angry when people faced with a negative or difficult to control situation (Anger Reaction). At the same time, the Anger Expression scores, especially "In", reflect that these patients tend to suppress, repress, deny anger feelings. Together with high Anger Control scores reflecting the expenditure of energy that people do to monitoring and control the expression of angry. Generally, people emotionally over-reactive with a high control of emotions experienced an internal conflict and become anxious and depressed especially if the situation causing anger persists. In this sample, males and females showed differently their emotional state of anger. Males tend to repress anger and show a lack of control of anger towards the outside, more than females. Adopting anger repression as the preferred mode of expression of anger could lead to depression and directly affects the immune system.

Nonetheless responses of anxiety, depression and anger seem to be organized into a pattern of a general emotional reaction. A first hypothesis is that worsening mood is associated with increased communication between the amygdala and hippocampus, which are linked to emotion and memory respectively. Probably due to individual and gender differences. Testosterone has been associated with increased emotional reactivity in the brain [18] and patient's personal history could explain why an anger mood (in the amygdala) became a trigger for the recollection of sad memories (in memory). In this framework patient's ability to control anger could be the defense that consent patient to feel better. And we have seen that this ability differs in males and females. From an immunological point of view, we know that there are different interconnections between emotions and immune response and between gender and immune response. Gender differences have also been reported recently in the response to immunotherapy treatments by Botticelli [19]. Many genes involved in the immune response are located on the X chromosome and gender and diet are implicated in differences in the function of microbiota in the modulate of the immune system. The study of specific differences between the sexes in the processing and reactions to emotions could have important implications for immunotherapy treatment use in cancer due to its different efficacy in males and females.

From an oncological point of view some serious considerations are to be taken on commitment at this time that immunotherapy is becoming an important cancer treatment. If we want to boost the body's natural defenses to fight cancer therefore the healthy immune systems became our primary concern. In conclusion, staff working in oncological day hospital should be trained to identify patients with emotional difficulties and facilitate referral for treatment. Today there is a growing interest in the use of patient-reported outcome measures that could capture some peculiar aspects that are not normally understood during the doctor-patient visit. Clinicians could gain important insights

about their patients by looking at the result of validated self-report patient questionnaires, to identify patients with inadequate expression of emotion or too high levels of emotional reaction in order to improve quality of care and a better response to treatment.

**Abbreviations:** CI, Confidence Interval; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; PD, progression of disease; QoL, quality of life; SD, standard deviation; STAXI, State-Trait Anger Expression Inventory.

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