Original Article

Fast time perception is associated with high levels of anxiety in cancer patients prior to starting chemotherapy

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SUMMARY   Our study explored the potential relationship between time perception and the level of anxiety in cancer patients prior to starting chemotherapy. Time perception was assessed in 162 chemonaïve patients with solid tumors by evaluating each subject's prospective estimation of how fast one minute passed compared to the actual amount of time passed. The median value of time perception was used to stratify the patients into two categories of fast and slow time perception. We used the generalized anxiety disorder questionnaire (GAD-7) as a screening tool for detecting levels of anxiety. Scores $\geq$ 10 were considered high. In total, 45 (27.8%) patients had high levels of anxiety. The pattern of the time perception distributions significantly changed according to the reported levels on the GAD-7 scale. Scores $\geq$ 10 correlated with fast time perception and the female gender. Patients with a fast time perception had significantly higher levels of anxiety (8.44 ± 5.1) than patients with a slow time perception (3.49 ± 4.3). ROC analysis revealed that at the optimal cut-off value of time perception, clinically significant levels of anxiety can be discriminated with an AUC = 0.78 (95% CI: 0.70-0.85, *p* < 0.001), a sensitivity of 82.2% and a specificity of 64.1%. Moreover, in a multivariate logistic regression model, fast time perception was an independent predictor of clinically significant levels of anxiety (OR: 8.24; 95% CI: 3.16-21.41, *p* < 0.001). Time perception is a novel potent indicator for high levels of anxiety in cancer patients.

Keywords   Oncology, cancer, anxiety, time perception

1. Introduction

Cancer patients are battling a life-threatening disease and experience severe treatment side effects that ultimately lead to high levels of distress as well as symptoms of depression and anxiety. Anxiety disorders are the most prevalent pathological conditions among cancer patients, with incidence rates ranging from 10 to 65% (*1,2*). Anxiety disorders are involved in cognitive, physiological and physical reactions as a response to unpleasant stimuli. Anxiety has been shown to cause many detrimental effects, such as fatigue, nonadherence to the prescribed treatment and poor overall quality of life (*3-5*). Cancer patients are preoccupied with stress-inducing events and experience anxiety symptoms due to fear of negative outcomes and treatment side effects (*6,7*). Despite these facts, several surveys showed that anxiety disorders and distress remained underdiagnosed and undertreated (*8-10*). Moreover there is not a specific cause leading to anxiety disorder, but only

population groups like cancer patients that are at risk of suffering it (*11-13*).

Time flows at different speed for each of us - an hour may fly-by, while a couple of minutes may seem to drag. There is a sound relation between a person's current emotional status and their perception of time: entertainment activities appear to accelerate time flow, while the monotony of uneventful circumstances seems to instinctively decelerate time (*14,15*). Subsequently, when time appears to flow rapidly, one is left with the impression that less time has passed than what the clock shows. Alternatively, when time seems to drag, we have the feeling that more time has passed than what the clock shows. Thus the emotional state is a crucial modifier of time perception (*16,17*). There are no reports in the literature on the relationship between the experience of time and the levels of anxiety reported by cancer patients.

To improve the detection of high levels of anxiety in busy clinical practices, we searched for a relationship

between time perception and levels of anxiety prior to starting chemotherapy.

2. Patients and Methods

2.1. Patient selection

Our report includes 162 in patients who were treated at the Clinic of Medical Oncology at MHAT "Nadezhda" Sofia and UMHAT "St. Marina" in Varna, Bulgaria, from February 2018 to January 2019. The inclusion criteria for the patients were as follows: the presence of histologically verified cancer, an age greater than 18 years, an understanding of the Bulgarian language, the absence of psychiatric disorders, and the absence of clinical conditions that could limit the patient's understanding of the provided materials and tasks. The exclusion criteria were as follows: patients who reported chronic use of drugs such as sedatives, stimulants, pain killers or opioids, and patients with decompensated chronic disease such as hypo- and hyperthyroidism, heart diseases, etc. None of the patients had limitations to their activities of daily life. Basic sociodemographic and clinicopathological data were collected, along with an assessment of anxiety with the GAD-7 (generalized anxiety disorder questionnaire) questionnaire and a measurement of time perception. The procedure was approved by the Scientific Research Ethics Committee of "Prof. Dr. Paraskev Stoyanov" at the Medical University in Varna and MHAT "Nadezhda", Sofia, Bulgaria.

2.2. Measurement of time perception

Time perception was assessed by the subjects' individual prospective estimations of how quickly one minute passed compared to the actual amount of time passed. Time perception assessment, was performed before patients' first medical appointment for chemotherapy initiation. The assessments were performed in separate research area by a dedicated specially trained study nurse. The patient received instructions to estimate a duration of one minute after a start signal. When the subject gave a stop signal, the interpreter stopped the chronometer, and the estimated time was recorded. For our patients, the estimation of one minute ranged from 7 to 90 sec. The median value of time perception (37 sec) was used to stratify the patients into the two categories of fast ($\leq$ median) and slow (> median) time perception.

2.3. Assessment of the levels of anxiety

The GAD-7 questionnaire was used to assess the levels of anxiety in cancer patients. The GAD-7 anxiety severity score is calculated by assigning the scores of 0, 1, 2, and 3 to the response categories of "not at all",

several days", "more than half the days" , and "nearly every day", respectively. In our study, the GAD-7 total score for the seven items ranges from 0 to 21: 0-4: minimal anxiety ($n = 73$); 5-9: mild anxiety ($n = 44$); 10-14: moderate anxiety ($n = 29$); and 15-21: severe anxiety ($n = 16$) (*18*). Moderate and severe anxiety were considered high levels of anxiety. The questionnaire was validated against other mental health measurements and against a mental health practitioner interview. A clinical cut-off of 10 was recommended for diagnosing generalized anxiety disorder with a sensitivity of 89% and a specificity of 82% (18). However, a later study evaluated GAD-7 as a broader instrument to test for any anxiety disorder and determined an acceptable AUC of 0.86. From this AUC, a lower cut-off of 8 for any anxiety disorder was recommended, which gave a sensitivity of 77% and a specificity of 82% (*19*).

2.4. Statistical analysis

Data were managed and analyzed using IBM SPSS Statistics software ver. 23. The Mann-Whitney U test, χ^2 test and Spearman correlation coefficients were used to compare and evaluate the relationship between the levels of anxiety and clinicopathological characteristics of the patients, such as age, gender, primary tumor location and time perception. For the interpretation of correlation test results, rho values were interpreted as follows, < 0.19, very weak; 0.19-0.39, weak; 0.40-0.59, moderate; 0.60-0.79, strong; and > 0.80 very strong. The diagnostic accuracy of the subjective time perception was also determined by obtaining the largest possible area under the curve (AUC) in receiver operating characteristic (ROC) curve analysis. Trends in the changes of time perception across different levels of anxiety were assessed using the Jonckheere-Terpstra test. The minimum sample size for regression analysis was determined to be 150 patients to provide 80% power at a 5% significance level. The calculation was based on the six covariates and a 40% proportion of positive cases (*20*). Odds ratios (ORs) with confidence intervals (CIs) for categorical outcomes were calculated using a binary logistic regression model. Nagelkerke R-Square is reported for the logistic regression analysis. A $p \leq 0.05$ (two-tailed) was considered significant.

3. Results

3.1. Patient characteristics

A total of 162 patients with malignant solid tumors participated in the study; 60 (37%) were men, and 102 (63%) were women. The median age was 62 years, and the mean age of the group was 59.3 ± 10.6 years with an age range of 27 to 78 years. The sample included subjects with a variety of cancer types: 25 (15.4%) cases of lung cancer, 60 (37%) cases of breast cancer,

38 (23.5%) cases of colorectal cancer, and 39 (24.1%, representing more than 10 different histology types) cases of other cancers. Detailed descriptions of the patients' characteristics can be found in Table 1.

Table 1. Sociodemographic and clinicopathological patient characteristics

Patient characteristics	n (%)
Sex	
Male	60 (37%)
Female	102 (63%)
Ethnicity	
Bulgarian	153 (94.4%)
Turkish	9 (5.6%)
Religion	
Christian	149 (92.0%)
Muslim	9 (5.6%)
Atheist	3 (1.9%)
Unspecified	1 (0.5%)
Marital status	
Married	110 (67.7%)
Not married	52 (32.3%)
Cancer type	
Lung cancer	25 (15.4%)
Breast cancer	60 (37.0%)
Colorectal cancer	38 (23.5%)
Other[*]	39 (24.1%)
Stage	
II and III	99 (61.5%)
IV	63 (38.5%)
Education level	
Secondary[**]	107 (66%)
Tertiary[***]	55 (34%)

[*]Other: more than 10 types of cancer. [**]Secondary: up to 13 years of education. [***]Tertiary: 13+ years of education.

3.2. Relationship between time perception, level of anxiety and patient characteristics

The mean anxiety score was 6.09 ± 5.3. A total of 45 (27.8%) patients had high levels of anxiety (cut-off ≥ 10), and their mean score was 13.2 ± 3.1. At a cut-off score of ≥ 8, 59 (36.4%) patients had high levels of anxiety with a mean score of 12.1 ± 3.4. A fast time perception and the female gender were related with high levels of anxiety (Table 2). Patients with breast cancer (7.48 ± 5.2) had significantly higher levels of anxiety in comparison to patients with colon cancer (4.07 ± 4.2) and trended towards higher anxiety levels compared to patients with lung (5.7 ± 5.8) and other (6.1 ± 5.5) types of cancer. Women (7.32±5.2) had significantly higher levels of anxiety than men (4.0 ± 4.7) ($p < 0.001$). No significant differences in the levels of anxiety were observed regarding age, marital status, education or stage of disease.

Women estimated one-minute intervals faster than men (33.3 ± 15.3 sec *vs.* 45.9 ± 17.9 sec; $p < 0.001$). No significant differences in time perception were observed regarding education level, marital status, stage of disease or type of cancer. Patients with a fast time perception had significantly higher levels of anxiety (8.44 ± 5.1) than patients with a slow time perception (3.49 ± 4.3) ($p = 0.001$) (Figure 1). Time perception differs significantly among patients with minimal ($n = 73$), mild ($n = 44$), moderate ($n = 29$) and severe anxiety ($n = 16$) (Figure 2). ROC analysis revealed that at the optimal cut-off value of time perception, patients with low and high anxiety levels can be discriminated with an AUC = 0.78 (95%

Table 2. Relationship between levels of anxiety and patient characteristics

Variable	Low anxiety, n (%) GAD score ≤ 10	High anxiety, n (%) GAD score ≥ 10	p	Low anxiety, n (%) GAD score ≤ 8	High anxiety, n (%) GAD score ≥ 8	p
Gender			< 0.001			0.001
Male	53 (88.3)	7 (11.7)		48 (80.0)	12 (20.0)	
Female	64 (62.7)	38 (37.3)		55 (53.9)	47 (46.1)	
Age			0.76			0.46
≤ 65	77 (71.3)	31 (28.7)		67 (62.0)	41 (38.0)	
> 65	39 (73.6)	14 (26.4)		36 (67.9)	17 (32.1)	
Marital status			0.58			0.49
Married	80 (73.4)	29 (26.6)		71 (65.1)	38 (34.9)	
Not married	36 (69.2)	16 (30.8)		31 (59.6)	21 (40.4)	
Cancer type			0.12			0.029
Lung cancer	20 (80.0)	5 (20.0)		17 (68.0)	8 (32.0)	
Breast cancer	37 (61.7)	23 (38.3)		30 (50.0)	30 (50.0)	
Colorectal cancer	31 (81.6)	7 (18.4)		30 (78.9)	8 (21.1)	
Other[*]	29 (74.4)	10 (25.6)		26 (66.7)	13 (33.3)	
Stage			0.58			0.75
II and III	70 (70.7)	29 (29.3)		62 (62.6)	37 (37.4)	
IV	47 (74.6)	16 (25.4)		41 (65.1)	22 (34.9)	
Time perception			< 0.001			< 0.001
Fast	46 (54.1)	39 (45.9)		37 (43.5)	48 (56.5)	
Slow	71 (92.2)	6 (7.8)		66 (85.7)	11 (14.3)	
Education level			0.68			0.78
Secondary[**]	76 (71.0)	31 (29.0)		67 (62.6)	40 (37.4)	
Tertiary[***]	41 (74.1)	14 (25.9)		35 (64.8)	19 (35.2)	

[*]Other: more than 10 types of cancer. [**]Secondary: up to 13 years of education. [***]Tertiary: 13+ years of education.
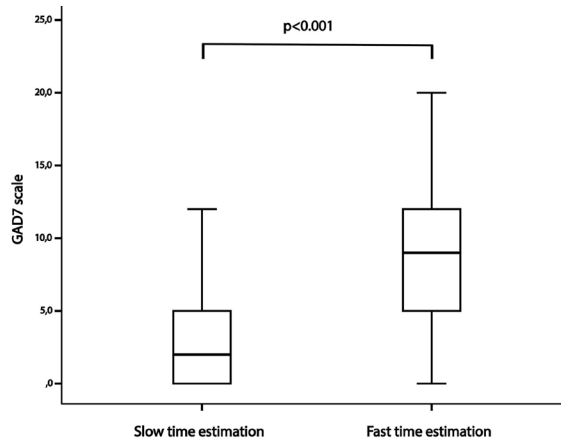
Figure 1. A bar graph depicting the level of anxiety in patients with slow and fast time perception. The Mann-Whitney U test was used to detect significant differences in the levels of anxiety between the groups.
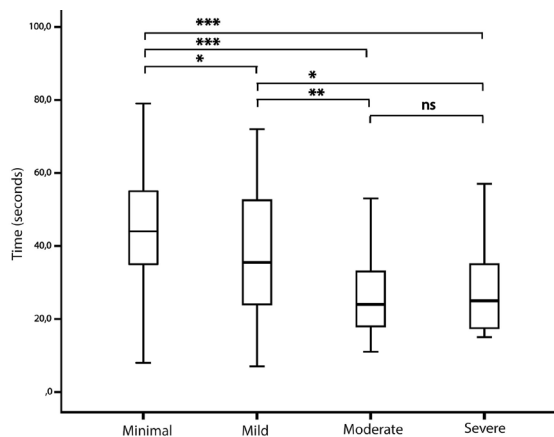

Figure 2. A bar graph depicting time perception among patients with minimal (n = 73), mild (n = 44), moderate (n = 29) and severe anxiety (n = 16). The Mann-Whitney U test was used to detect significant differences in the levels of anxiety between the groups; *indicates p value < 0.05, **indicates p value < 0.01 and ***indicates p value < 0.001.

CI: 0.70-0.85, $p < 0.001$) and with a sensitivity of 82.2% and specificity of 64.1% (Figure 3A). When we used the median as a cut-off the sensitivity and specificity was 86.7% and 60.7% respectively. A similar AUC = 0.74 was found when we used a GAD-7 score cut-off of ≥ 8 for high levels of anxiety (Figure 3B). There was a moderate, negative correlation (Spearman rho = -0.48, $p < 0.001$) between time perception and levels of anxiety.

3.3. Predictors of high levels of anxiety

In a univariate logistic regression analysis of women, patients with fast time perception and breast cancer were associated with high levels of anxiety. In a stepwise backward multiple logistic regression model, the female gender and fast time perception were independent predictors of high levels of anxiety (Table 3). In addition, the model accounted for 30.9% (Nagelkerke) of the variance in anxiety level. Similar results were found when we used a GAD-7 score cut-off of ≥ 8 for high levels of anxiety. These results were confirmed in an ordinal logistic regression model, where dependent factors were the four levels of anxiety (minimal, mild, moderate and severe) and time perception was used as a continuous independent covariate (data not shown).

4. Discussion

In this study, we investigated the association between time perception and levels of anxiety among patients with malignant solid tumors. The subjective passage of time was faster in patients with moderate and severe anxiety. The prospective time perception test revealed that patients with a faster perception of time were associated with an increased risk of high levels of anxiety.

A cancer diagnosis can lead to detrimental effects on physical and mental health. The diagnosis can
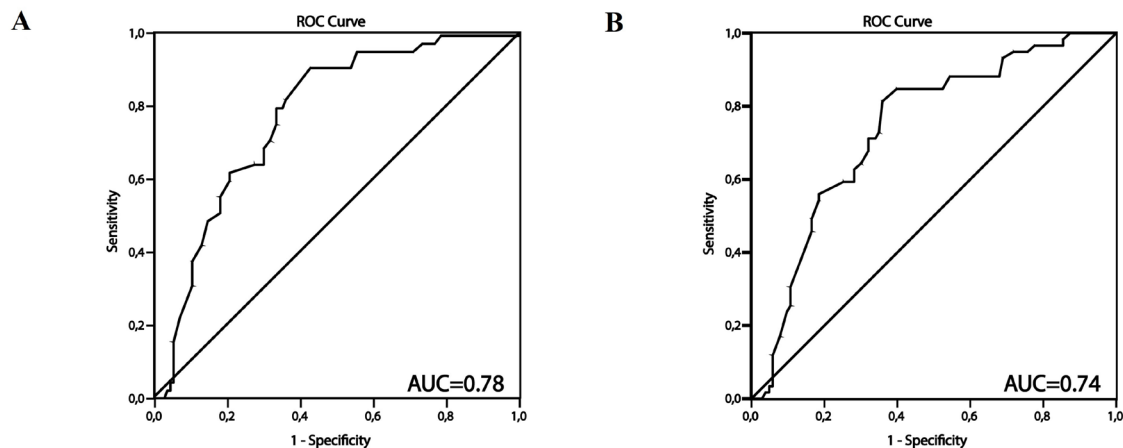

Figure 3. Receiver operating characteristic (ROC) curve analysis in which time perception was used to differentiate between patients with low and high levels of anxiety. The diagnostic accuracy of time perception was determined by obtaining the largest possible area under the curve (AUC) in ROC analysis. **(A)**, GAD-7 scores ≥ 10 were considered high levels of anxiety, AUC = 0.78 (95% CI: 0.70 - 0.85, $p < 0.001$); **(B)**, GAD-7 scores ≥ 8 were considered high levels of anxiety, AUC = 0.74 (95% CI: 0.66 - 0.81, $p < 0.001$).

Table 3. Univariate and stepwise backward multivariate regression analyses for predicting high anxiety levels (GAD-7 scores ≥10)

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Age						
≤ 65 y *vs.* > 65 y	0.89	0.42-1.86	0.76			
Gender						
Women *vs.* Men	4.46	1.85-10.28	0.001	3.01	1.16-7.77	0.023
Cancer type						
Breast cancer	2.26	1.12-4.53	0.02			
Stage						
IV *vs.* II and III	1.27	0.59-2.48	0.59			
Marital status						
Married *vs.* Not married	0.81	0.39-1.68	0.58			
Time perception						
Fast *vs.* slow	10.03	3.9-25.5	< 0.001	8.24	3.16-21.41	< 0.001
Education						
Secondary* *vs.* Tertiary**	1.16	0.56-2.43	0.68			

*Secondary: up to 13 years of education. **Tertiary: 13+ years of education.

negatively affect social functioning and inevitably cause distress over the course of the disease. A meta-analysis showed that a combination of mood disorders can occur in 30-40% of patients admitted to a hospital (*21*). Numerous papers have shown that the most important risk factors for anxiety are low socioeconomic status, low educational level, poor physical health, gender, type of cancer and age (*22-26*). Approximately 30% of these patients needed medical interventions (*27*), and these high levels of anxiety were not transient but remained for a longer period of time in more than 20% of patients (*28*). Stress and anxiety lead to neuroendocrine changes that can negatively affect patient outcomes (*29,30*). Thus, improving the early diagnosis of anxiety may lead to better survival and quality of life. The time point before the start of chemotherapy was identified as one of the most anxiety-provoking time periods and may call for interventions (*31*). Our method for assessing time perception by prospective estimation of a one-minute interval is relatively simple and fast to perform. It ensures higher compliance for both the patient and physician and avoids emotions inevitably linked to one's past or future. To the best of our knowledge, the present study is the first to discover an association between fast perception of time and high levels of anxiety among patients with solid tumors prior to starting chemotherapy. The need for additional predictive factors to explain the variations seen in self-reports of anxiety is well-known (*2*). Time perception has the potential to be such a factor, and because of this potential relationship, our model reached an R^2 value of more than 0.30.

Clinical practice is in need of a reliable, reasonably-priced and effective mechanism to recognize people who may gain from a further or more profound assessment. Our research suggests the conditional estimation of one-minute time intervals as a new possible indicator of anxiety in cancer patients. The suggested method ensures an efficient fast screening for abnormally high anxiety levels in cancer patients. It is a proven fact that a great number of patients do not report their actual levels of anxiety due to frustration or concern of being slandered for having a mental issue (*32*). Moreover, oncologists are not psychologists; they often lack the skills and/or training to tackle emotional issues. In view of the above, a basic screening tool that can be used in the intense everyday environment of a regular clinical practice is gravely needed. Under such circumstances, reviewing the perception of time by means of the method suggested by us can enable physicians to effectively detect patients at risk due to elevated anxiety levels.

Research data shows that the perception of speed of time in patients with advanced cancer is different from that in patients with no evidence of the disease, i.e., to patients suffering from advanced cancer a week seemed to pass much more slowly than to those who had no evidence of the disease (*33*). A recent study shows that the level of distress undoubtedly affects time perception and its distribution patterns. The one-minute time period of evaluation, suggested herein, is therefore a new efficient marker of elevated levels of distress in cancer patients (*34*). All things considered, time perception can be affected by the circumstances - personality, state of mind and level of activity during the testing period are just few of them. Assessments made at longer time periods may prove quite inaccurate and unreliable (*35*). We as humans tend to estimate "short" intervals of time as longer and "long" time durations as shorter (*36*). Time perception results can be made more accurate in an experimental setting similar to ours in which patients were expected to estimate time duration (*37*). Numerous psychophysical methods have been used in various studies for assessing the perceived duration of a time interval. The outcomes, however, have been inconsistent and incomparable. The

data collected as well as the interpretations that come with it, have often been inconsistent and contradictory (*38*). It is common belief that time goes quickly only when you are having fun. This idea was questioned in an experimental model, where the estimation of time appeared faster when participants were awaiting a negative experience (*39*). Consistent with this finding, our results suggest that time perception appeared faster for patients with high levels of anxiety before starting their treatment, which is often with uncertain outcome.

Several limitations of our study should be noted. First, the GAD-7 scale focuses only on 1 anxiety disorder, even though there are many patients with other anxiety disorders, such as social phobia and posttraumatic stress disorder, who also need clinical attention. Clinicians and researchers usually do not look for depression or anxiety alone. Considering the frequency with which depression and anxiety occur together (up to 60%), a search for one condition should always be accompanied by an assessment of the other. Nevertheless, GAD is one of the most common mental disorders seen in outpatient practices. The Global Burden of Disease Study examined major depressive and anxiety disorders separately, and it was reported that anxiety disorders are the seventh most burdensome condition of all diseases worldwide today (*12*). Our study is cross-sectional and thus accurate predictions cannot be definitely made. Another limitation of our study is that the GAD-7 scale provides only probable diagnoses that should be confirmed by further evaluation.

It is well-known that the diagnosis of anxiety disorders is challenging due to a lack of objective biomarkers, and the diagnosis is based only on symptoms (*40*). Our study proposes a potential marker for anxiety for the first time, and further studies are warranted to confirm our results. Emotional concerns are a risk factor for nonadherence to treatment. Thus, early identification of such concerns is crucial for developing a management plan. The method we propose for detecting emotional concerns is an easily performed, time-saving, nonintrusive, ultrashort screening tool that is even suitable for patients who are not willing to reveal their level of anxiety via direct questionnaires.

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