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„PROF. DR PARASKEV STOYANOV“ - VARNA

DEPARTMENT OF ONCOLOGY

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**THE RELATIONSHIP BETWEEN DISTRESS AND
TIME PERCEPTION IN CANCER PATIENTS**

DISSERTATION SUMMARY

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1. Abbreviations

NCCN - National Comprehensive Cancer Network

DT – Distress thermometer

PS – performance status

ECOG – Eastern Cooperative Oncology Group

AUC – area under the curve

ROC - Receiver operating characteristic

OR – Odds ratio

CI - Confidence interval

SD – Standard deviation

HADS – Hospital Anxiety and Depression Scale

PDI – Psychological distress inventory

PHQ2 – Patient Health Questionnaire

PL – Problem List

PTSD – Post-traumatic stress disorder

SSRI – Selective serotonin reuptake inhibitor

SI - Système international d'unités

WHO – World Health Organization

2. Introduction

With the rising incidence of malignant tumors globally, the scientific community strives to develop not only better diagnostic and therapeutic methods towards cancer itself, but also towards delivering better care for the psychosocial consequences of the disease. Diagnosis of cancer leads to deleterious effects on the patient's psychological well-being and social functioning which ultimately results in distress. Psychological distress covers a wide spectrum, ranging from normal feelings of vulnerability, sadness and fears to problems that can become disabling, such as depression, anxiety, extensive worries, negative thoughts, or social isolation. Distress is not only a transient mood change, but a disabling condition which negatively affects patient's quality of life. The National Comprehensive Cancer Network (NCCN) defines distress as a „multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional) social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment”. Distress can lead to unfavorable disease outcomes unless appropriate therapeutic measures are taken. These negative effects are due to reduced patient compliance to the

prescribed treatment, low level of satisfaction with the received healthcare services, and overall worse quality of life in distressed patients. Current guidelines for distress management include screening for distress directed towards all patients, ideally at every medical visit, or at a minimum at their initial visit and as clinically indicated, especially if there is a change in their disease status (i.e. remission, recurrence, progression or treatment related complications). If distress remains undetected by the treating physician, then no appropriate therapeutic interventions (pharmacological and non-pharmacological) can be applied in order to alleviate patient's psychoemotional burden. Distress levels can be assessed with NCCN's Distress Thermometer (DT) which is usually administered together with the Problem List (PL) – a short questionnaire which identifies key issues of concern in cancer patients. The clinical application of the Distress Thermometer was studied in patients with different types of cancer and it has shown good sensitivity and specificity in finding clinically significant levels of distress.

People subjectively perceive the passage of time at different speeds – an hour may pass extremely quickly, whereas a few minutes may seem to drag for an eternity. There is a strong connection between one's current emotional state and one's experience of time – distraction by entertaining activities seems

to speed up time, while boredom during uneventful situations is associated with subjective slowing down of time. If time is perceived as passing quickly then the person underestimates the real time interval measured by a stopwatch, and vice versa. Cognitive models of time estimation suggest that an individual's perception of time depends on an internal clock, with a pacemaker that produces subjective time units. In these cognitive models, subjective time units are registered only at moments when attention is drawn to the passage of time. There is a lack of targeted research in the literature on the relationship between the perception of time and levels of distress in cancer patients.

The present study focuses on the potential relationship between time perception and distress in cancer patients prior to initiation of systemic antineoplastic cancer treatment.

3. Aim and objectives of the dissertation

3.1 Aim of the study

The aim of the present study is to investigate the relationship between time perception and levels of distress in patients with malignant solid tumors.

3.2 Objectives

1. To select patients with malignant solid tumors who are referred for initiation of systemic antineoplastic therapy.
2. To assess the level of distress in patients who gave their consent to participate in the study.
3. To compare the levels of distress in study participants with the accumulated global data.
4. To assess the perception of time in the patient sample.
5. To collect main clinicopathological characteristics of the patient sample.
6. To assess correlations between levels of distress, perception of time and various clinicopathological characteristics.
7. To determine the specificity and sensitivity of prospective one-minute time estimation test as an indicator of distress level.
8. To identify predictors for high levels of distress.

4. Hypotheses

Based on previous research and the developed cognitive models on time perception, a hypothesis was formulated, which states that cancer patients with slow subjective perception of time (i.e. patients who have faster time estimation results in prospective tests) are going to be more distressed.

Block and Zakay developed an „attentional gate“ cognitive model which postulates that during prospective time estimation, an internal pacemaker produces subjective time units which are registered only when attention is drawn towards the passage of time. The more subjective time units are registered, the longer the time interval is perceived. Cancer patients' minds are preoccupied with thoughts about their illness and its associated symptoms, the period of treatment and its side effects, fear of death and other negative emotions. Based on the “attentional gate” cognitive model a hypothesis was made which postulates that psychoemotional distress in cancer patients draws their attention away from meaningful thoughts and redirects it towards the passage of time. In the absence of meaningful and constructive thoughts, the capability of cancer patients to distract themselves from keeping track of time diminishes which

leads to a greater amount of registered time units and a subjective feeling that time passes more slowly.

The hypothesis of the present study states that patients with a slower subjective perception of time (i.e. faster prospective estimation of time intervals) are going to have higher levels of distress. It was assumed that a prospective one-minute time estimation test can be used as an ultra-short screening tool for distress screening in patients with cancer.

5. Materials and methods

5.1 Center of research

Clinic of Medical Oncology – University Multiprofile Hospital for Active Treatment “Sveta Marina” – Varna, Bulgaria.

5.2 Patient population

A prospective non-interventional single center study was conducted. A total of 262 patients were recruited during the period of August-2016 till December-2017. Patients were considered eligible if all of the inclusion criteria and none of the exclusion criteria were met.

Inclusion criteria:

1. Age \geq 18 years at the time of study entry.
2. Histologically verified malignant solid tumor.
3. Initiation of first cycle systemic antineoplastic therapy for malignant cancer.
4. Proficiency in Bulgarian language.

Exclusion criteria:

1. History of another primary malignancy.
2. Severe uncontrolled concomitant diseases.

3. CNS diseases associated with cognitive deficit.
4. Diseases or conditions that could limit the patient's understanding of the provided materials or tasks.

5.3 Collected information

The following information was collected in an electronic database for each of the patients in the trial:

Demographic data:

- *ID number / Initials*
- *Age*
- *Sex: male/female*
- *Marital status: single / married / widowed / divorced*
- *Ethnicity: Bulgarian / Turkish*
- *Religion: atheist / Christian / Muslim / unspecified*

Clinical and pathological information:

- *Localization of primary tumor*
- *TNM and clinical stage*
- *Performance status (PS) according to Eastern Cooperative Oncology Group (ECOG) (Table. 1)*
- *Date of initial cancer diagnosis*
- *Intercurrent diseases*

Table. 1 Assessment of performance status according to Eastern Cooperative Oncology Group (ECOG) scale, adapted from Robert L. Comis, MD, Group Chair.

Grade	ECOG (PS) – performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

5.4 Assessment of distress levels

In accordance with NCCN's guidelines for distress management, in the present study the levels of distress were assessed with the Distress Thermometer (Appendix 2). DT is a validated self-administered tool which is convenient for quick screening. Patients are asked to indicate the number that best describes how much distress they have experienced over the past week, on a visual analogue scale ranging from 0 (no distress) to 10 (extreme distress). A meta-analysis of 42 studies with more than 14 000 patients with cancer found the pooled sensitivity of DT to be 81% and the pooled specificity to be 72% at a cut-off score of 4. Based on the result from DT, patients were divided into two groups: patients with low levels of distress (DT score ranging from 0 to 3) and patients with high levels of distress (DT score greater than 4).

5.5 Assessment of subjective time perception

Subjective time perception was assessed by the subject's individual prospective estimation of how fast one minute passed compared to the actual time. The patient receives instructions to estimate a duration of one minute after a start signal. When the subject gives a stop signal, the interpreter stops the chronometer,

and the estimated time is recorded. In the studied cohort of patients, the estimation of one-minute time interval ranged from 9 to 92 seconds. The median value of time estimation (40 seconds) was used to stratify the patients into two groups: fast (\leq median) and slow ($>$ median) time estimation. It is important to note that patients with a measured fast time estimation (measured externally by the interpreter) actually have a subjective sensation of slow passage of time, and vice versa. Throughout the discussion of the results in the present study the externally measured by the interpreter time estimation will be presented.

5.6 Statistical design and analysis

Data were managed and analyzed using IBM SPSS Statistics Software ver. 23. All values are presented as a median value \pm one standard deviation (SD). In all tests p value < 0.05 (two-tailed) was considered significant.

For management of acquired data the following statistical methods were used:

- 1.** Statistical data grouping method – collected variables are grouped in variational, interval, categorical, ordinal and scalar statistical series depending on their type.

2. Descriptive methods:
 - central tendency assessments – used to calculate the mean, median and mode of continuous variables.
 - interval assessments – used to calculate significance – p. When the p coefficient equals 0.95 (95%), the probability of type I error is 0.05 (5%).
 - confidence intervals (CI) - a 95% confidence interval was used which is interpreted as the probability that the specified interval contains the actual point estimate in the general population.
3. Graphical methods – line and surface area charts were used along with pie charts, boxplot graphs and histograms.
4. Nonparametric analysis –
 - Pearson χ^2 (chi-squared) test was used for assessment of statistically significant differences between categorical variables.
 - Assessment of associations between a categorical variable with two groups and an ordinal or continuous variable was made with Mann-

Whitney U test and Student t-test depending on data's distribution.

- Assessment of associations between a categorical variable with more than two groups and an ordinal or continuous variable was made with Kruskal-Wallis H test.
- Assessment of associations between an ordinal variable and an ordinal or continuous variable was made with Jonckheere-Terpstra test.

5. Correlation analysis – Spearman coefficient for linear correlation was computed. The correlation coefficient rho can assume values between -1 and +1, and the sign depends on the direction of association. The following scale was used for interpreting the degree of association:

< 0.19 – very weak correlation;

0.19 ÷ 0.39 – weak correlation;

0.40 ÷ 0.59 – moderate correlation;

0.60 ÷ 0.79 – strong correlation;

≥ 0.80 – very strong correlation;

6. The diagnostic accuracy of prospective one-minute time estimation test as a tool for distress assessment was determined by obtaining the largest possible area

under the curve (AUC) in receiver operating characteristic (ROC) analysis. The following scale of AUC was used for interpreting the degree of accuracy:

≥ 0.9 – excellent

$0.8 \div 0.9$ – good

$0.7 \div 0.8$ – fair

< 0.7 – poor

7. Predictors for high levels of distress were determined using regression analysis – univariate and stepwise-backward multivariate logistic regression analyses. Odds ratios (OR) with confidence intervals (CI) were calculated. The adequacy of the model used in regression analysis was determined by calculating Nagelkerke R-Squared. The minimum sample size for regression analysis was determined to be 200 in order to provide 80% power at a 5% significance level.

6. Results

6.1 Descriptive analysis of patient characteristics

A total of 262 patients with malignant solid tumors participated in the study - 116 were male (44.3%) and 146 were female (55.7%). The median age was 62 years, and the mean age of the group was 59.8 ± 11.23 years, with an age range between 29 and 81 years. The sample included subjects with a variety of cancer types: 65 (24.8%) lung cancer patients, 67 (25.6%) breast cancer patients, 66 (25.2%) colorectal cancer patients and 64 (24.4%) patients with other types of cancer (more than 14 different histology types). Detailed description of patient characteristics is available in Table 2. The distribution of sociodemographic and clinicopathological patient characteristics is illustrated in Figures 1-7.

Table 2 Sociodemographic and clinicopathological patient characteristics

Sex	
Male	116 (44.3%)
Female	146 (55.7%)
Ethnicity	
Bulgarian	244 (93.1%)
Turkish	18 (6.9%)
Religion	
Christian	180 (68.7%)
Muslim	16 (6.1%)
Atheist	40 (15.3%)
Unspecified	26 (9.9%)
Marital status	
Single	18 (6.9%)
Married	181 (69.3%)
Widowed	35 (13.4%)
Divorced	28 (10.3%)
Performance status	
0	118 (45%)
1	144 (55%)
Cancer type	
Lung cancer	65 (24.8%)
Breast cancer	67 (25.6%)
Colorectal cancer	66 (25.2%)
Other (more than 14 different types)	64 (24.4%)
Stage	
II and III	121 (46.2%)
IV	141 (53.8%)

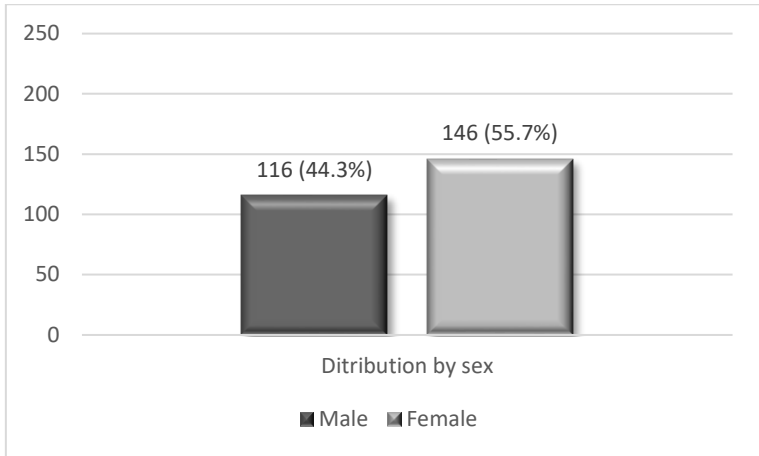


Figure 1. Bar graph depicting patient distribution by sex.

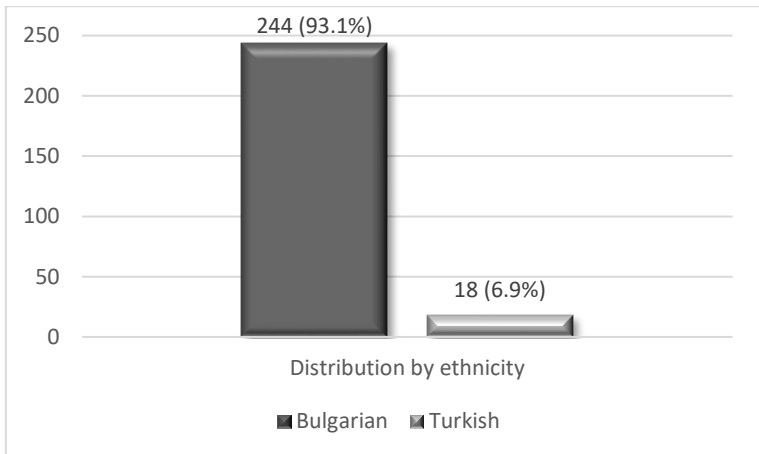


Figure 2. Bar graph depicting patient distribution by ethnicity.

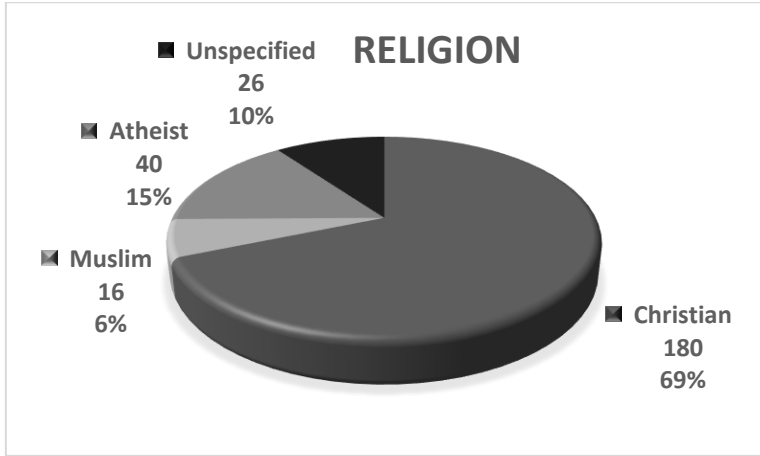


Figure 3. Pie chart depicting patient distribution by religion.

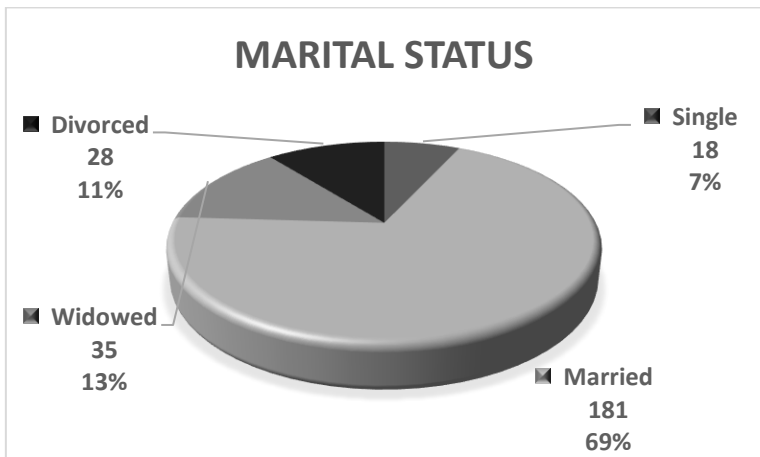


Figure 4. Pie chart depicting patient distribution by marital status.

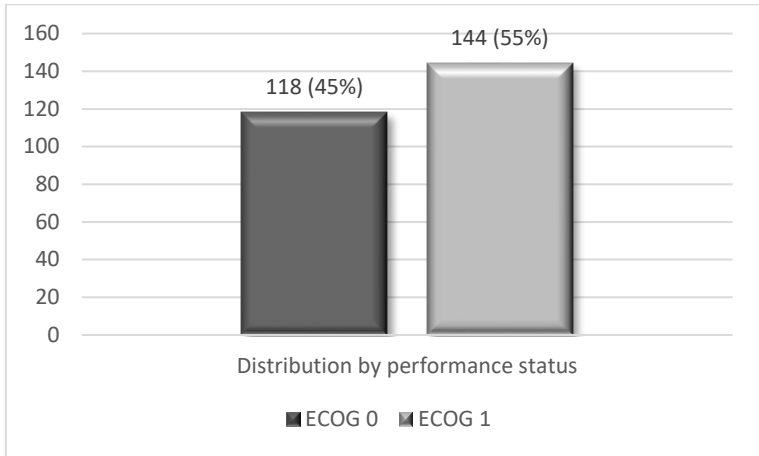


Figure 5. Bar graph depicting patient distribution by ECOG performance status.

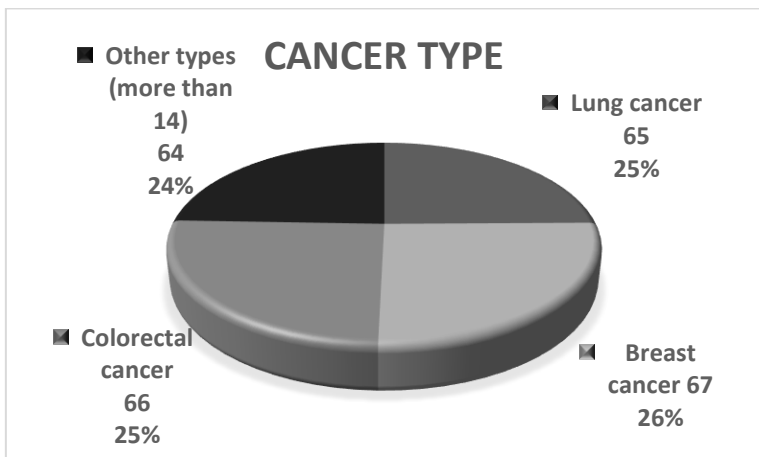


Figure 6. Pie chart depicting patient distribution by cancer type.

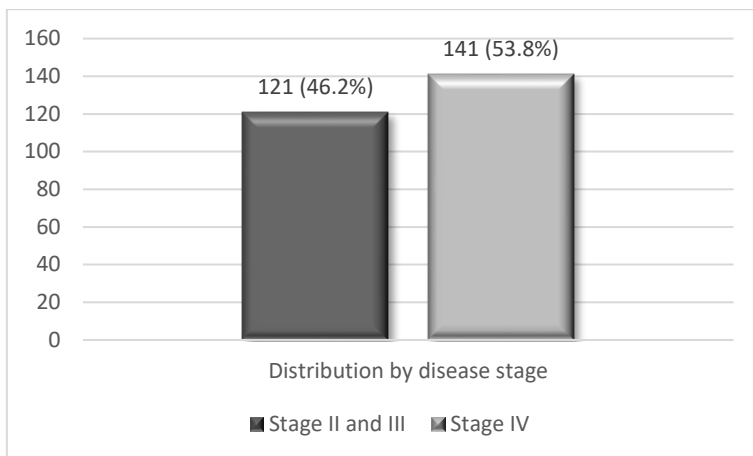


Figure 7. Bar graph depicting patient distribution by disease stage.

6.2 Correlation analysis between time perception, distress level and patient characteristics

The mean distress score assessed with NCCN's DT was 3.94 ± 3.07 . A total of 136 (51.9%) patients had high distress and their mean distress score was 6.45 ± 1.9 . The following factors were associated with high levels of distress: fast time estimation, ECOG PS 1, lung cancer and breast cancer (Table 3). A strong trend towards high level of distress was observed in younger patients (≤ 62 years) ($p = 0.051$).

Table 3 Correlations between level of distress and patient characteristics

	Low distress, n (%)	High distress, n (%)	p
Sex			0.294
Male	60 (47.6%)	56 (41.2%)	
Female	66 (52.4%)	80 (58.8%)	
Age			0.051
≤ 62 years	58 (46%)	79 (58.1%)	
> 62 years	68 (54%)	57 (41.9%)	
Ethnicity			0.19
Bulgarian	120 (95.2%)	124 (91.2%)	
Turkish	6 (4.8%)	12 (8.8%)	
Religion			0.10
Atheist	23 (18.3%)	17 (12.5%)	
Christian	80 (63.5%)	100 (73.5%)	
Muslim	6 (4.8%)	10 (7.4%)	
Unspecified	17 (13.5%)	9 (6.6%)	

Marital status			0.15
Single	4 (3.2%)	14 (10.4%)	
Married	90 (71.4%)	91 (67.4%)	
Widowed	18 (14.3%)	17 (12.6%)	
Divorced	14 (11.1%)	13 (9.6%)	
Performance status			0.021
0	66 (52.4%)	52 (38.2%)	
1	60 (47.6%)	84 (61.8%)	
Cancer type			0.002
Lung cancer	20 (15.9%)	45 (33.1%)	
Breast cancer	30 (23.8%)	37 (27.2%)	
Colorectal cancer	36 (28.6%)	30 (22.1%)	
Other (more than 14 different types)	40 (31.7%)	24 (17.6%)	
Stage			0.486
II and III	61 (48.4%)	60 (44.1%)	
IV	65 (51.6%)	76 (55.9%)	
Time perception			0.010
Fast time estimation	54 (42.9%)	80 (58.8%)	
Slow time estimation	72 (57.1%)	56 (41.2%)	

The distress levels of patients with lung cancer (5.05 ± 3.12) and breast cancer (4.36 ± 3.01) did not differ significantly ($p = 0.19$). Both groups had significantly higher levels of distress than patients with colorectal cancer (3.2 ± 2.8) or patients with other types of cancer (3.13 ± 2.8) (Figure 8).

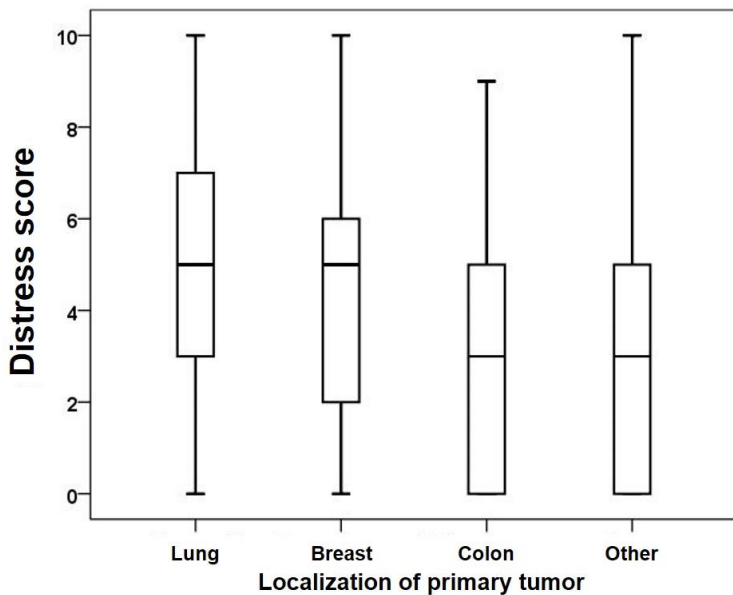


Figure 8. Box plot graph depicting level of distress by tumor localization ($p < 0.05$, Kruskal-Wallis test).

Patients with PS 1 (4.15 ± 2.9) did not have significantly higher levels of distress than patients with PS 0 (3.68 ± 3.2) ($p = 0.15$) (Figure 9).

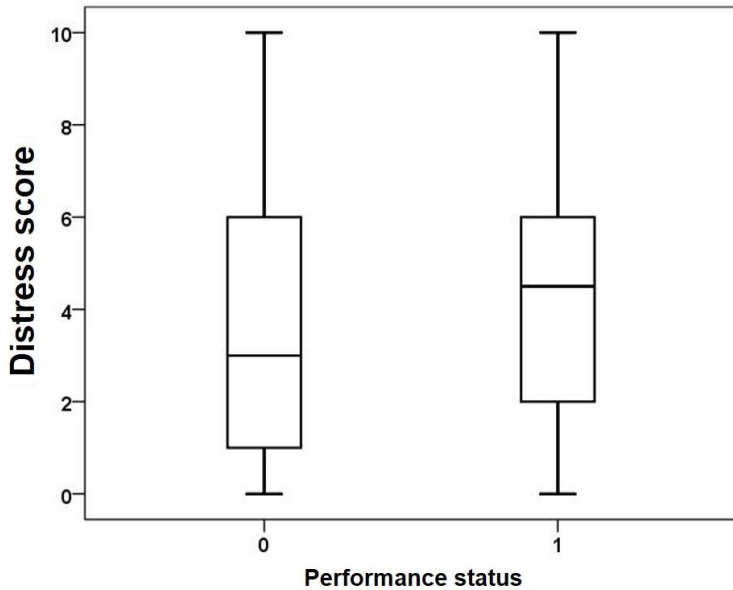


Figure 9. Box plot graph depicting level of distress by patient's performance status ($p = 0.15$, Mann-Whitney test).

Women (4.36 ± 3.2) had significantly higher levels of distress than men (3.41 ± 2.8) ($p = 0.02$) (Figure 10).

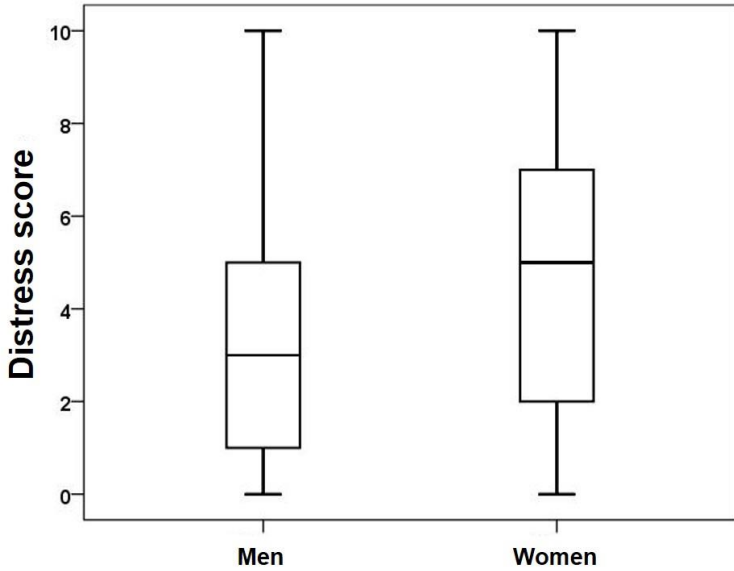


Figure 10. Box plot graph depicting distress levels by patient's sex. ($p = 0.02$, Mann-Whitney test).

Patients younger than 62 years (4.31 ± 2.9) had significantly higher levels of distress than patients older than 62 years (3.52 ± 3.1) ($p = 0.024$) (Figure 11).

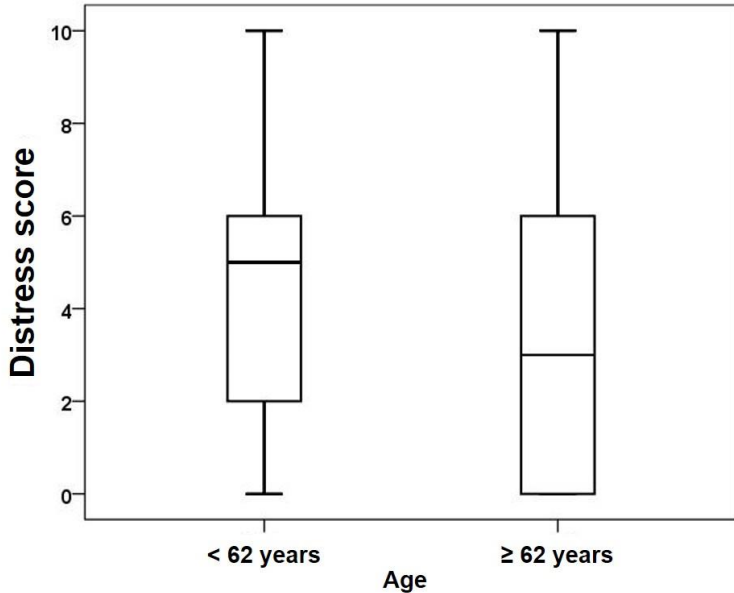


Figure 11. Box plot graph depicting level of distress by patient's age ($p = 0.024$, Mann-Whitney test).

No significant differences in the levels of distress were observed with respect to ethnicity, religion, marital status and stage of the disease. (Figure 12).

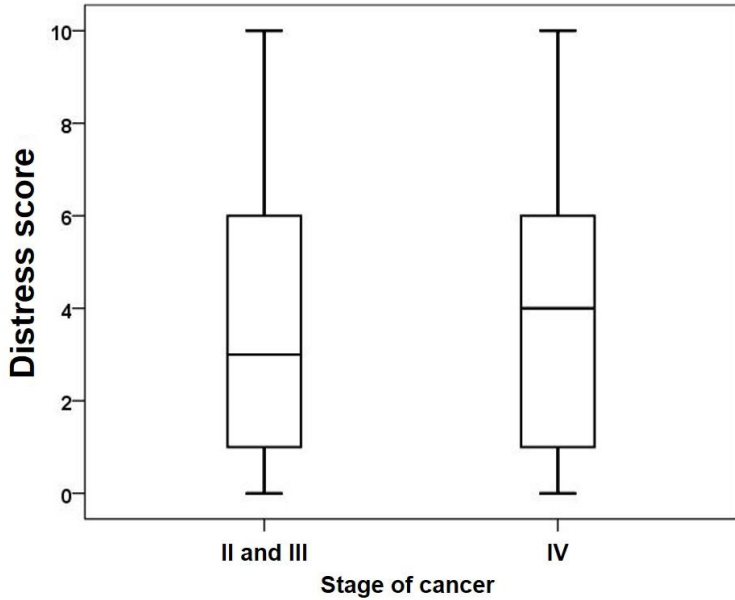


Figure 12. Box plot graph depicting level of distress by patient's stage of the disease ($p > 0.05$, Mann-Whitney test).

In the studied patient population fast time estimation was associated only with the levels of distress ($p = 0.010$), sex ($p = 0.038$) and marital status ($p = 0.009$) (Table 4).

Table. 4 Correlations between perception of time and patient characteristics

	Slow time estimation, n (%)	Fast time estimation, n (%)	p
Sex			0.038
Male	65 (50.8%)	51 (38.1%)	
Female	63 (49.2%)	83 (61.9%)	
Age			0.818
≤ 62 years	66 (51.6%)	71 (53%)	
> 62 years	62 (48.4%)	63 (47%)	
Ethnicity			0.381
Bulgarian	121 (94.5%)	123 (91.8%)	
Turkish	7 (5.5%)	11 (8.2%)	
Religion			0.387
Atheist	21 (16.4%)	19 (14.2%)	
Christian	87 (68%)	93 (69.4%)	
Muslim	5 (3.9%)	11 (8.2%)	
Unspecified	15 (11.7%)	11 (8.2%)	
Marital status			0.009
Single	6 (4.7%)	12 (9%)	
Married	89 (70.1%)	92 (68.7%)	
Widowed	12 (9.4%)	23 (17.2%)	
Divorced	20 (15.7%)	7 (5.2%)	

Performance status			0.405
0	61 (47.7%)	57 (42.5%)	
1	67 (52.3%)	77 (57.5%)	
Cancer type			0.335
Lung cancer	29 (22.7%)	36 (26.9%)	
Breast cancer	29 (22.7%)	38 (28.4%)	
Colorectal cancer	33 (25.8%)	33 (24.6%)	
Other (more than 14 different types of cancer)	37 (28.9%)	27 (20.1%)	
Stage			0.440
II and III	56 (43.8%)	65 (48.5%)	
IV	72 (56.3%)	69 (51.5%)	
Distress			0.010
Low level of distress	72 (56.3%)	54 (40.3%)	
High level of distress	56 (43.8%)	80 (59.7%)	

No significant differences in time perception were observed with respect to age, ethnicity, religion, stage of the disease and performance status. A trend for faster time estimation in women (39.6 ± 16.2 sec) compared to men (43.3 ± 16.6 sec) ($p = 0.091$) was observed (Figure 13).

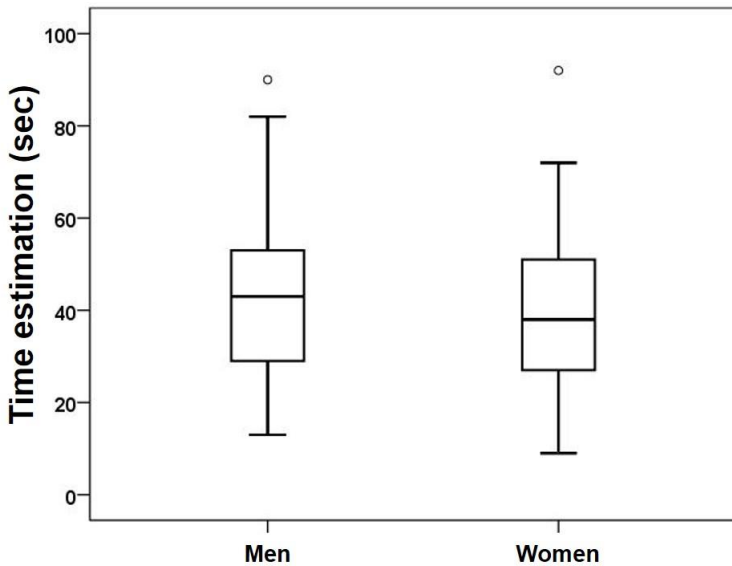


Figure 13. Box plot graph depicting time estimation by patient's sex ($p = 0.091$, Mann-Whitney test).

Kruskal-Wallis test did not discover statistically significant differences in time perception among patients with different localizations of the primary tumor ($p = 0.367$) (Figure 14).

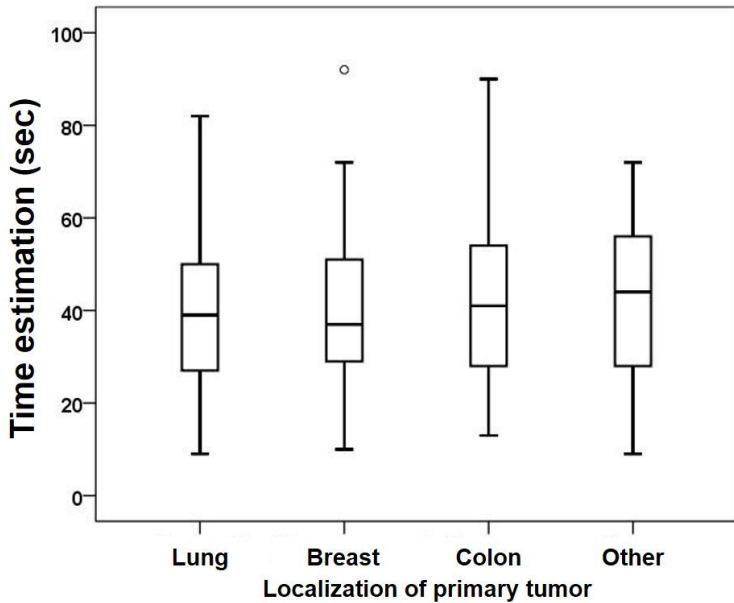


Figure 14. Box plot graph depicting time perception among patients with different localizations of their primary tumors ($p = 0.367$, Kruskal-Wallis test).

Patients with a fast time estimation had significantly higher levels of distress (4.55 ± 3.1) than patients with a slow time estimation (3.3 ± 2.9) ($p = 0.001$) (Figure 15).

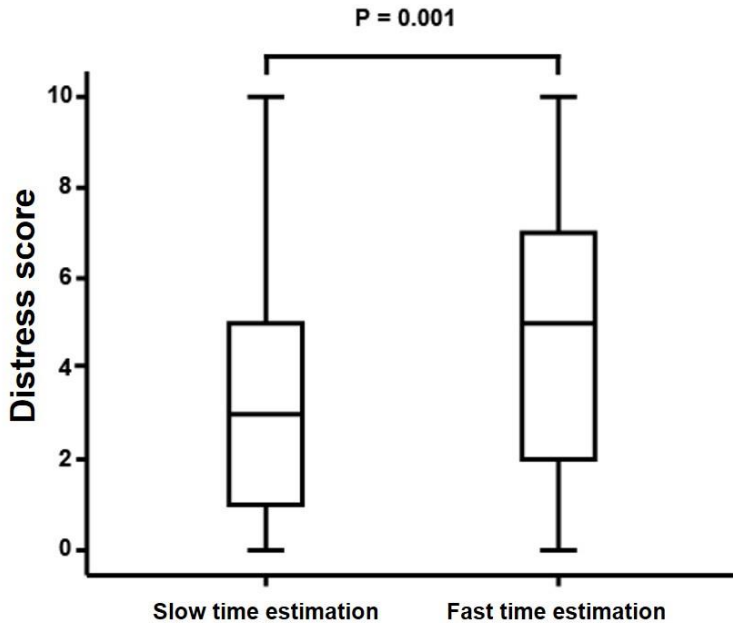


Figure 15. Box plot graph depicting levels of distress in patients with slow and fast time estimation of one-minute time interval ($p=0.001$, Mann-Whitney U test).

A Jonckheere-Terpstra test for ordered alternatives showed that there was a statistically significant trend for faster median values of time estimation with higher levels of distress ($p = 0.001$) (Figure 16).

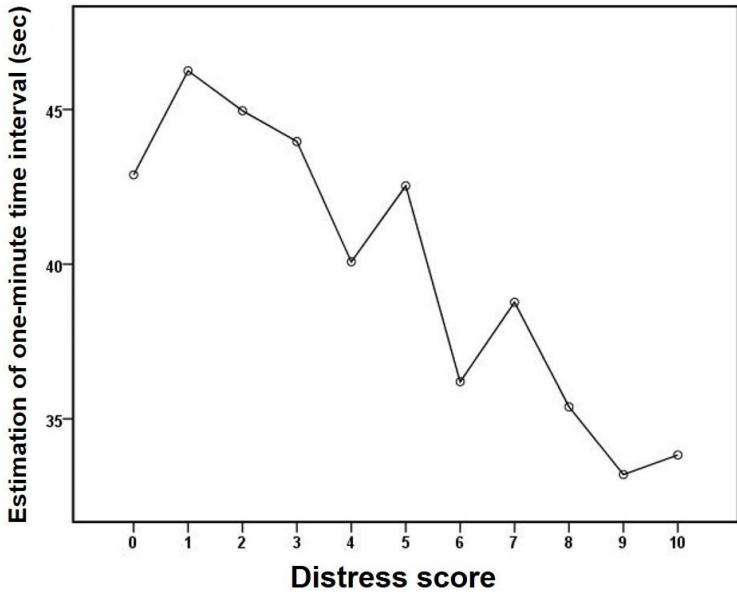


Figure 16. Graph showing median time perception (assessed with prospective one-minute estimation test) at each level of distress.

ROC analysis revealed that at the optimal cut-off value of time estimation, patients with low and high distress levels can be discriminated with an AUC = 0.60 (95% CI: 0.53 ± 0.07, p = 0.005) and with a sensitivity of 62.5% and specificity of 53.2% (Figure 17).

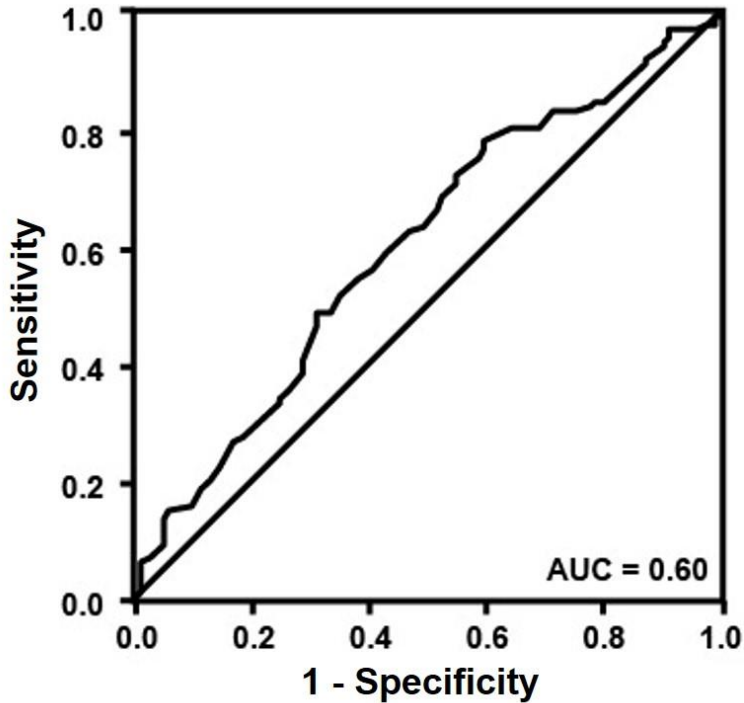


Figure 17. Receiver operating characteristic (ROC) analysis in which time estimation was used to differentiate between patients with low and high levels of distress. The diagnostic accuracy of time estimation was determined by obtaining the largest possible area under the curve (AUC) in ROC analysis.

There was a weak, but statistically significant, negative correlation between time estimation and level of distress (Spearman rho = -0.191, p = 0.002) (Figure 18).

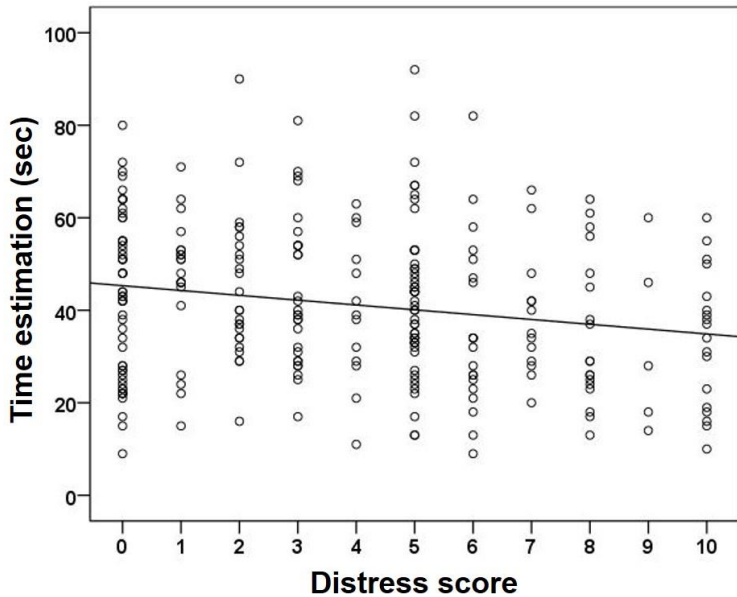


Figure 18. Correlation analysis between time estimation and distress levels. There is a weak negative correlation between time estimation and level of distress (Spearman rho = -0.191, p = 0.002).

6.3 Predictors of a high level of distress

In univariate logistic regression analysis, patients with a fast time estimation, lung or breast cancer, or PS 1 were associated with an increased risk of high levels of distress (Table 5).

In regression analysis patients were grouped in the following way: religious (Christian, Muslim, unspecified) and non-religious (atheist); married and nonmarried (single, widowed, divorced).

In a stepwise-backward multivariate logistic regression model, fast time estimation, lung and breast cancer, PS 1, and age < 62 years were independent predictors of high levels of distress (Table 6). In addition, the model accounted for 15.4% (Nagelkerke) of the variance in distress status.

Table. 5 Univariate logistic regression analysis for predicting high level of distress.

Variable	Univariate analysis		
	Odds ratio	95% CI	p
Age ≤62 years vs >62 years	1.62	0.097-2.64	0.051
Sex Male vs Female	0.77	0.47-1.25	0.29
Cancer type Lung cancer	3.75	1.80-7.78	<0.001
Breast cancer	2.05	1.02-4.13	0.043
Performance status 0 vs 1	1.77	1.08-2.96	0.022
Religion Religious vs non-religious	0.64	0.32-1.26	0.19
Marital status Married vs nonmarried	1.2	0.71-2.05	0.48
Ethnicity Bulgarian vs Turkish	1.93	0.70-5.32	0.20
Time estimation Fast vs slow time estimation	1.905	1.166-3.11	0.010

Table. 6 Multivariate regression analysis for predicting high level of distress.

	Multivariate analysis		
Variable	Odds ratio	95% CI	p
Age ≤62 years vs >62 years	1.82	1.062-3.120	0.026
Cancer type Lung cancer	3.503	1.631-7.52	0.001
Breast cancer	2.24	1.05-4.78	0.036
Performance status 0 vs 1	1.97	1.12-3.46	0.017
Time estimation Fast vs slow time estimation	1.97	1.06-2.98	0.029

7. Discussion

The incidence of malignant tumors rises globally, which stimulates the invention of novel and better diagnostic and therapeutic methods for management of cancer. In recent years, increasing amount of attention is given to the improvement of patients' quality of life and the psychosocial consequences of the disease and its treatment. Making the diagnosis of cancer inevitably leads to deterioration of patients' mental health and social functioning which leads to distress.

In the present study, a total of 262 patients with malignant solid tumors were surveyed, out of which 136 (51.9%) had high levels of distress, as measured with NCCN's Distress Thermometer. These data are consistent with the gathered information globally – according to different studies, between 20% and 52% of patients with cancer experience significant amounts of distress. The relatively high incidence of distress in our patient sample could be explained by the lack of effective nation-wide program for distress management in cancer patients in Bulgaria. There are differences in the prevalence of clinically significant distress in different geographic regions. In Bulgaria there are no large-scale studies of distress levels in cancer patients, and there are no studies that follow NCCN's guidelines

for screening with the use of the Distress Thermometer. A Bulgarian study that surveyed 65 cancer patients before surgical treatment for their disease, found that high levels of distress were present in 14% of men and 72% of women. In that study the patient sample is too small, and the authors note that the localization of the primary tumors is not balanced across both sexes. The study in this dissertation is the first large-scale research of distress levels in Bulgarian patients with malignant solid tumors. The survey included all patients who gave informed consent ,who met all of the inclusion criteria and none of the exclusion criteria and who began their first cycle of systemic antineoplastic therapy in the Clinic of Medical Oncology at UMHAT Sveta Marina – Varna. The recruitment period was between August 2016 and December 2017. This made the formation of a representative unbiased patient sample possible.

Previous research shows that among the most important risk factors for high levels of distress are sex, age, marital status, stage of the disease, social status and type of cancer. The results from the present study confirm that younger patients, those with poor performance status, lung cancer and breast cancer are with higher risk for significant distress. Globally, the results regarding different risk factors for distress are not homogenous.

There are inconsistent reports about the influence of age, education, marital status and stage of the disease on distress levels. These discrepancies may be due to different methods used for distress assessment and due to different measurement timepoints during the course of the disease.

According to the results of our study, clinically significant levels of distress (DT score ≥ 4) are experienced by 48.3% of men and 54.8% of women. In our patient sample women (4.36 ± 3.2) had significantly higher levels of distress than men (3.41 ± 2.8). These results are consistent with previous research on the influence of sex on distress, globally. Higher distress levels are found not only in women with cancer, but also in the general population. The reasons behind the differences in distress in both sexes are not adequately studied, but possible explanations include biological, social and demographic influences and the difference between internalization and externalization in both sexes.

In the present study, within the group of patients with high distress, 58.1% are younger than 62 years. Patients younger than 62 years (4.31 ± 2.9) have higher levels of distress compared to those older than 62 years (3.52 ± 3.1). These results are consistent with available data that distress is higher in younger patients. Possible explanations for this relation are greater

disturbances in everyday activities in younger patients (related to work, family, children and social contacts), and already present comorbidities and greater capacity to accept illness in older patients. There are reports that these higher levels of distress in younger patients are only present during the period of diagnosis of cancer and that the difference between both age groups diminishes over the course of the disease due to better adaptation mechanisms in younger patients. Our research could not investigate this phenomenon due to the design of the study and measurement of distress in only one timepoint.

In the studied population no significant differences in distress levels were found regarding marital status (married / single / widowed / divorced). In univariate and multivariate regression analyses single, widowed and divorced patients were grouped together and compared to married patients. Despite such grouping marital status was not found to be a predictor for distress levels in the studied sample. Most of the available results worldwide show higher levels of distress in single cancer patients. The explanation behind this relationship lies in the emotional support that is given by the patient's spouse. Other studies including ours fail to identify a correlation between marital status and distress levels. Such heterogeneity in the results could be explained by the differences in the studied

populations and cultural variations related to relationships inside the family. The present study collects information about marital status from the available medical documentation. It is possible that some of the patients are living together with a partner which is not reflected in the official categories of marital status. In this way, the opportunity to assess the effect of emotional support provided by the partner on the levels of distress is missed.

In our studied patient sample, 44.1% of patients with ECOG performance status 0 had high levels of distress, while 58.3% of patients with ECOG PS 1 had high distress assessed by NCCN's Distress Thermometer. In univariate and multivariate logistic regression analyses ECOG performance status is a significant predictor for high distress levels. Data from previous research confirm the association between poor performance status and high distress levels. Worse performance status reflects the patient's lower functional capacity (for work, self-care, and mobility) and the patient's greater dependence on caretakers. This inevitably results in higher distress.

In the present study no associations between distress levels and patient's ethnicity and religion were found. There is published data, that patients from minority ethnicities experience greater distress. In our patient sample, information about ethnicity was taken based on self-determination. Only

6.9% (n = 18) of patients reported ethnicity different than Bulgarian, which did not provide enough power to statistically identify differences in distress levels depending on the ethnicity. The data accumulated so far regarding religion and distress in cancer patients are contradictory. Religion / spirituality can enhance the patient's individual adaptive abilities as well as expand access to psychosocial care within the religious community. However, some negative religious reactions (anger towards God, feelings of abandonment by God, or perception of diagnosis as God's punishment) have been shown to be associated with higher levels of distress. In the present study, the majority of patients were Christian and only a small proportion of cancer patients were atheists, Muslim or unspecified, which did not allow for an adequate analysis of religion as a risk factor for distress. Also, only religious affiliation was assessed, but not the degree of religiosity.

According to worldwide data 37.9% - 61.6% of patients with lung cancer, 32.8% - 51.8% of patients with breast cancer and 28.7% - 53.9% of patients with colorectal cancer have high distress levels. In the present study, the incidence of high distress among patients was 69.2% for lung cancer patients, 55.2% for breast cancer patients, and 45.4% for colorectal cancer patients, respectively, which correlates with data from previous studies.

There are results in the world literature that the incidence of clinically significant high distress levels increases with more advanced stage of cancer. Surprisingly, the results of the present study showed that patients with metastatic (stage IV) and non-metastatic disease (stages I, II and III) had similar levels of distress. These results suggest that the treatment team should provide more information to patients about the stage of their disease and the chances of complete recovery in order to reduce distress in non-metastatic patients. However, according to a study, only 44.9% of cancer patients know the true stage of their disease, but the levels of distress in the study population correlated with the actual stage of the disease and not with the patient's assumed stage.

Despite the high incidence of distress in cancer patients, distress often remains unrecognized by the treatment team. This failure to diagnose distress, subsequently does not allow for appropriate measures to be taken, which in turn leads to reduced quality of life for both patients and relatives, reduced adherence to prescribed treatment, longer hospitalizations, higher direct and indirect medical costs and reduced survival.

Linking distress levels to patient survival is a topic of great scientific interest. Distress and cancer are thought to affect each other on the principle of positive feedback loop. More advanced

stage of cancer and more pronounced symptoms inevitably lead to higher levels of distress. Distress, in turn, affects the course of the disease - by reducing compliance with treatment or by biological mechanisms.

The diagnosis of malignancy and its subsequent treatment impose significant cognitive and emotional demands on patients. These requirements reduce the individual's ability to adapt and this leads to increased somatic reactivity to stressors and to stress-induced neurocognitive disorders. The combination of distress and reduced adaptability can lead to emotional disturbances, depression, cognitive dysfunction and ultimately to reduced work capacity, unemployment, family problems, social isolation and reduced quality of life. The influence of distress on cancer patients is due to two-way interactions between psychosocial and biological factors. The main levels of interactions are the brain, the endocrine system (mostly the hypothalamic-pituitary-adrenal axis) and the immune system. The normal biological response to stressors includes the secretion of norepinephrine, adrenaline and cortisol, for which almost all cells in the human body have receptors. Psychosocial distress also provokes similar biological effects - it increases basal cortisol levels and reduces acute cortisol reactivity. This leads to dysregulation of the immune system and a state of

chronic inflammation. Stress-induced dysregulation of the immune system affects the course of the malignancy in three main ways: suppresses the protective immune response, induces / exacerbates chronic inflammation, and enhances immunosuppressive signals. There is evidence that distress may reduce cellular immune function by affecting NK cells. These effects promote invasive tumor growth, tumor neoangiogenesis, suppress apoptosis and help to avoid the recognition of tumor cells as foreign to the immune system, which ultimately stimulates the progression and metastasis of cancer (Figure 19).

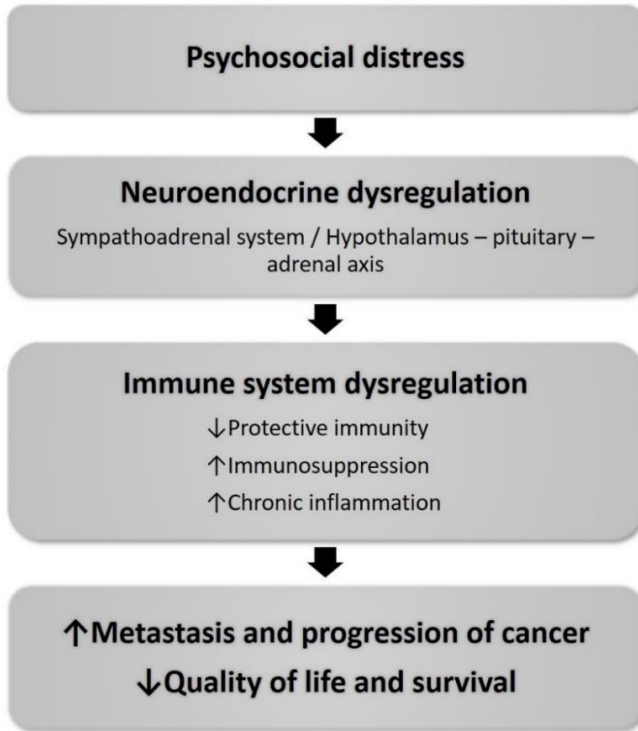


Figure 19. Biological mechanisms by which psychosocial distress influences the course of cancer and patient survival.

The above outlines the urgent need to implement algorithms and standards for distress management. Given the importance of the problem and in an attempt to stimulate awareness among treatment teams, different authors often label distress as the "sixth vital sign" – along with blood pressure, temperature, respiratory rate, heart rate and pain.

Distress screening has low specificity compared to structured clinical interviews for the diagnosis of psychiatric disorders. The NCCN team deliberately targets distress as an object of screening because it is a non-stigmatizing concept that encompasses a wider range of patient responses to cancer and its treatment. Distress ranges from normal experiences to psychopathology. The purpose of NCCN's group is not to identify all available psychiatric comorbidities in patients, but to identify those patients who would benefit from psychosocial support. Recommendations for screening and treatment of distress have been developed, but their implementation and efficient utilization is problematic.

The low levels of distress diagnosis are explained by several factors, including lack of training for oncologists and nurses to diagnose this condition and lack of time to perform screening. The lack of recognition of distress and the subsequent lack of measures to address it are worrying, because the available psychosocial support methods are highly effective in reducing distress, improving quality of life, improving compliance with cancer treatment and controlling the symptoms of the disease.

The need for efficient screening tool for distress arose after global recommendations introduced distress screening as part of routine clinical practice. Screening methods need to be fast, easy

to use, circumvent patients' fear of stigmatization about their psycho-emotional problems, and quickly screen out patients who need additional interventions. Along with the imposed Distress Thermometer as a standard screening tool from the NCCN guidelines, in the thesis we propose the use of an innovative new method for assessing the perception of time as a predictive marker for high levels of distress.

In the dissertation study for the first time globally a connection between the perception of time and the levels of distress in cancer patients (measured by NCCN's Distress Thermometer), is proved. Faster estimation of one-minute time interval (i.e. slower subjective perception of time) is significantly correlated with higher levels of distress in cancer patients. Faster time estimation is a predictive marker for high levels of distress in the performed univariate and multivariate regression analyses. The proposed time perception test can be used as a screening method to detect high levels of distress in patients with malignancies with satisfactory sensitivity and specificity. These results correlate well with the developed "attentional-gate" cognitive model for the perception of time and the assumption that patients with existing distress focus their attention on the elapsing time, which leads to the registration of more subjective time units and a subjective feeling of slower

passage of time. The results confirmed the hypothesis that patients with high levels of distress would have a slower subjective perception of time. In the literature overview it was pointed out that the perception of time was studied mainly in the context of psychiatric illnesses. The results of studies on the subjective perception of time in patients with affective and anxiety disorders are not homogenous, probably due to different patient populations and differences in the assessment methods used.

Although between 30% and 40% of patients with malignant tumors suffer from various psychiatric illnesses, the dissertation targets distress as an object of study given the fact that it covers a wider range of patient reactions to the disease - from normal to psychopathological.

The perception of time is influenced by many factors such as momentary physiological state, personality traits and activity during the study. The test proposed in the dissertation for assessment of perception of time by prospectively estimating a one-minute time interval is relatively simple and easy to perform. That way the method provides better compliance on both sides - patient and doctor. Estimation of longer time intervals is associated with greater variability and inaccuracy. Usually people overestimate short time intervals (in the order of

seconds) and underestimate longer intervals (in the order of hours). In experimental settings such as the one proposed in the dissertation, the assessment of time perception is more accurate when participants are informed that they are about to track time periods. Researchers in the field of perception of time offer different tests for its evaluation, but the results between the different studies are not comparable nor homogeneous with each other. The results collected so far, and their explanations are often contradictory.

The method proposed in the dissertation for assessment of perception of time is a novel predictive marker for distress in patients with malignant diseases. The proposed test is practical and quickly screens out patients at risk for high distress. Existing questionnaires and scales have completion rates between 49% and 97.5%. Many patients do not report their true levels of distress due to feeling of shame about the presence of a psychological problem and fear of stigmatization. Also, a relatively small number of oncologists are trained to recognize and discuss the emotional problems of their patients. For these reasons, a large proportion of patients with high distress remain unrecognized. A systematic review of the available screening methods highlights the problems associated with differences in the used terminology, the measured variables, the format and

length of the tests. All this proves the need for a simple screening method that is easy to apply in the busy daily clinical practice. In these situations, assessment of perception of time through the method proposed in the dissertation can help treatment teams to easily identify patients at risk for high distress.

The proposed ultra-short screening method for distress by prospective estimation of a one-minute time interval demonstrated an area under the curve (AUC) of less than 0.7, suggesting poor differentiation between patients with high and low distress. However, in clinical practice, most existing psychological tests have AUC values in the range of 0.7-0.8. It is considered that if a questionnaire has an AUC above 0.9, then the results are most likely due to an error in the design of the method and not due to good validity of the test. One of the disadvantages of the scientific work is that the proposed test is compared only with NCCN's Distress Thermometer, which, although a validated method, is still only a rapid screening test. Of interest for future research is the comparison of one-minute time interval estimation test with other more comprehensive and frequently used tests for assessment of distress in cancer patients such as: Hospital Anxiety and Depression Scale (HADS), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), General

Health Questionnaire (GHQ-28), Brief Symptom Inventory (BSI-18).

Another disadvantage of the scientific work is the lack of a control group of healthy people. According to some scientific reports, the perception of time accelerates with age in healthy individuals. The analysis of the collected results does not show a significant difference in the perception of time according to the patient's age. Due to the lack of a control group with healthy individuals, it was not possible to answer the question whether this normal tendency for acceleration of perception of time with age is disrupted by underlying diseases such as cancer.

During the course of the scientific research, several areas were identified that would be of interest for future research. According to currently accumulated global data, high levels of distress are associated with lower survival - due to behavioral factors and psychoneuroimmunological mechanisms. Overall survival is a main primary endpoint in the majority of clinical trials in oncology. Survival is a direct measure of clinical benefit to the patient - it is a reliable and objectively measurable indicator, which is why, according to the FDA, it is the gold standard for a primary endpoint in cancer clinical trials. The dissertation proposes that the assessment of perception of time can be used as a test to detect high levels of distress. In future

research, it could be examined whether there is a relationship between the perception of time and survival, similar to the relationship between distress and survival found in previous studies. Such study would require a well-planned design to control for the many known predictors of overall survival - a sufficient number of patients with homogeneous characteristics should be recruited including homogenous carcinoma type, stage and other specific predictors according to the selected organ localization of the primary tumor.

Of interest for further research is the follow-up of the effect of various psychosocial, pharmacological and non-pharmacological methods used for the treatment of high levels of distress. Screening and detection of patients with clinically significant levels of distress is the first step in the overall management of distress. Subsequently, the patient should be referred to trained specialists for the application of appropriate and individualized therapeutic measures with a scientifically proven effect. There are results in the literature on the beneficial effects on distress levels with the right therapeutic approach. In future studies, it could be examined whether the decrease in distress levels assessed by the distress thermometer correlates with a corresponding change in patients' subjective perception of time.

The study in the dissertation demonstrates for the first time a relationship between the perception of time (measured by prospective estimation of a one-minute time interval) and distress levels (measured by NCCN's Distress Thermometer) in patients with malignant solid tumors prior to initiation of systemic antineoplastic therapy. Distress is a risk factor for non-adherence to treatment and could adversely affect patient survival. Therefore, there is a need for early detection of patients with high levels of distress in order to implement the necessary therapeutic interventions. Although our proposed method for detecting distress has low sensitivity and specificity, it is an easily performed, time-saving, and nonintrusive ultrashort screening tool that is even suitable for patients who are not willing to reveal their level of distress via direct questionnaires.

8. *Summary*

In summary, the most important contribution in the present study is the discovery of a relationship between perception of time (assessed by a prospective estimation of one-minute time interval) and levels of distress, quantified with NCCN's distress thermometer. The results show that fast time estimation is a statistically significant predictor of high distress levels in patients with malignant solid tumors prior to initiation of systemic antineoplastic therapy. As far as we know, this is the first study in the world to identify a relationship between subjective time perception and levels of distress in patients with solid tumors. For the first time in Bulgaria, a large scale screening for distress in cancer patients was conducted. Analysis of collected data shows correlations between distress, perception of time and main demographic and clinicopathological characteristics in our patient sample. We have found predictive markers for high distress levels which could potentially direct screening procedures specifically towards patients in higher risk. Our proposed ultrashort test of prospective one-minute time interval estimation manages to discriminate between patients with low and high distress with satisfactory accuracy.

Early identification of patients with high distress levels is crucial for subsequent administration of timely therapeutic interventions. Early diagnosis and treatment of distress improves patients' quality of life, improves compliance with treatment and the overall prognosis of the disease. Given the increased workload of healthcare personnel and lack of enough resources in the healthcare system, more efforts are put into finding quick and efficacious screening tests for distress. The stigma associated with cancer diagnosis and the presence of a psychological problem makes the process of development of screening tests difficult, because of low completion rates among patients, who find the tests unacceptable. Our proposed ultrashort screening test for distress levels by estimation of a one-minute time interval is easily performed, timesaving and it is a nonintrusive way to distinguish between patients with low and high distress with satisfactory accuracy.

9. *Conclusions*

1. It was discovered that more than 51.9% of patients with malignant solid tumors in our study have high levels of distress (measured with NCCN's Distress Thermometer) which is consistent with worldwide data. This could negatively impact their quality of life, treatment process and prognosis.
2. The following factors are associated with a greater risk of significantly higher distress levels:
 - subjective prospective estimation of one-minute time interval ≤ 40 seconds
 - age < 62 years
 - ECOG performance status = 1
 - lung cancer
 - breast cancer
3. No association was found between distress levels on one hand, and patients' sex, ethnicity, religion, marital status and stage of the disease on the other hand.
4. Significantly higher levels of distress were found in patients with lung and breast cancer, in contrast to patients with colorectal and other types of cancer.

5. Women exhibited significantly higher levels of distress than men.
6. Patients with metastatic and nonmetastatic disease were equally distressed. These findings suggest that the oncologist must provide more information and clarifications about patients' stage and associated outcomes to decrease their levels of distress and improve their quality of life.
7. In the studied patient sample fast time estimation correlated only with distress levels. No significant differences were found regarding ethnicity, religion, marital status, stage of the disease and age. There was a trend towards faster time estimation in women.
8. Patients with fast time estimation of one-minute time interval (i.e. patients with slow subjective feeling of passage of time) have significantly higher distress levels than patients with slow time estimation.
9. Assessment of time perception by prospective estimation of one-minute time interval can be used as an ultrashort screening tool for distress level

assessment with sensitivity of 62.5% and specificity of 53.2% (AUC = 0.60).

10. There is a weak but significant negative correlation between time perception and distress level, i.e. the faster time estimation is, the higher distress level is.

11. In univariate logistic regression analysis, the following predictors for high distress levels were found:

- fast time estimation of prospectively assessed one-minute time interval
- breast cancer
- lung cancer
- ECOG performance status = 1

12. In multivariate logistic regression analysis, the following predictors for high distress levels were identified:

- fast time estimation of prospectively assessed one-minute time interval
- breast cancer
- lung cancer
- ECOG performance status = 1
- age < 62 years

10. Contributions

1. For the first time worldwide, a relationship between distress levels in cancer patients (assessed with NCCN's Distress Thermometer) and perception of time (assessed with prospective one-minute time estimation test) was demonstrated.
2. For the first time worldwide, correlations between demographic and clinicopathological characteristics of cancer patients, their distress levels and their perception of time were identified.
3. For the first time worldwide, assessment of time perception by prospective estimation of one-minute time interval is proposed as a novel ultrashort screening tool for distress in cancer patients. This tool has an advantage because it avoids stigmatizing terms and it potentially has a higher rate of completion among patients.
4. For the first time in Bulgaria, a large-scale scientific study is being conducted on the levels of distress in cancer patients with solid malignant tumors.
5. For the first time in Bulgaria, a large-scale study is being conducted on the relationship between demographic and clinico - pathological characteristics of cancer patients and predictive markers for high levels of distress are being determined.

11. Publications and participations in scientific forums related to the dissertation

Publications:

1. **One-minute time interval estimation as a novel ultrashort tool for distress screening**

Nikolay Vladimirov Conev, Ivan Shterev Donev,
Dragomir Svetozarov Stoyanov

Journal: Supportive Care in Cancer, Pages: 2031-2037,

Publisher: Springer Berlin Heidelberg, Publication

date: 01.06.2019

2. **One-minute time interval estimation as a novel potent indicator of emotional concerns in cancer patients prior to starting chemotherapy**

Ivan Shterev Donev, **Dragomir Svetozarov Stoyanov**,
Teodorika Vitalinova Panayotova, Martina Stoyanova
Ivanova, Yavor Kostadinov Kashlov, Merlin Erol
Efraim, Nikolay Vladimirov Conev

Journal: Current Psychology, Pages: 1-7, Publisher:

Springer US, Publication date: 11.07.2019

3. Скрининг за дистрес при онкологично болни

Мартина С. Иванова, Асен И. Янчев, Николай В. Цонев, Иван Щ. Донев, Елеонора Г. Димитрова, Драгомир С. Стоянов, Явор К. Кашлов, Камелия Ж. Братоева, Станислава П. Пенева

Journal: Studia Oncologica, Pages: 31-39, Publisher: Парадигма, Publication date: 2018

4. Скрининг за дистрес при онкологично болни пациенти и фактори, повлияващи нивото му

Асен И. Янчев, Мартина С. Иванова, Елеонора Г. Димитрова, Иван Щ. Донев, Николай В. Цонев, Драгомир С. Стоянов, Явор К. Кашлов, Весела З. Златева, Камелия Ж. Братоева, Иван С. Александров, Станислава П. Павлова

Journal: Списание на Българското онкологично дружество, Pages: 82-90, Publisher: Българско онкологично дружество, Publication date: 2018

Participations:

1. Time perception as a novel ultra-short screening tool for distress in cancer patients.

Nikolay Vladimirov Conev, Ivan Shterev Donev, **Dragomir Svetozarov Stoyanov**, Martina Stoyanova Ivanova, Eleonora Georgieva Dimitrova, Asen Ivanov Yanchev

2018 ASCO Annual Meeting, 1-5 June 2018, Chicago, Illinois;

Source: Journal of Clinical Oncology; Volume: 36; Issue: 15_suppl; Pages: e22123-e22123; Publisher: American Society of Clinical Oncology; Publication date: 20.05.2018

2. One-minute time interval estimation as a novel potent indicator of need for help in cancer patients prior to starting chemotherapy.

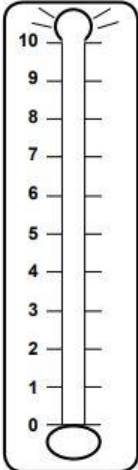
Dragomir Stoyanov, Ivan Donev, Nikolay Vladimirov Conev, Teodorika Panayotova, Martina Ivanova

2019 ASCO Annual Meeting, 31 May - 4 June 2019, Chicago, Illinois;

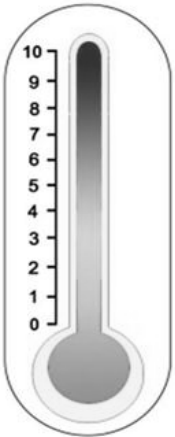
Source: Journal of Clinical Oncology; Volume: 37; Issue: 15_suppl; Pages: e23161-e23161; Publisher: American Society of Clinical Oncology; Publication date: 20.05.2019

12. Appendices

Appendix. 1 Distress thermometer and Problem list – NCCN, original English version

<p>NCCN DISTRESS THERMOMETER</p> <p>Instructions: Please circle the number (0–10) that best describes how much distress you have been experiencing in the past week including today.</p> <p>Extreme distress</p>  <p>No distress</p>	<p>PROBLEM LIST Please indicate if any of the following has been a problem for you in the past week including today. Be sure to check YES or NO for each.</p> <table border="0"> <tr> <td>YES</td> <td>NO</td> <td>Practical Problems</td> <td>YES</td> <td>NO</td> <td>Physical Problems</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Child care</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Appearance</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Housing</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Bathing/dressing</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Insurance/financial</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Breathing</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Transportation</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Changes in urination</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Work/school</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Constipation</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Treatment decisions</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Diarrhea</td> </tr> <tr> <td></td> <td></td> <td></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Eating</td> </tr> <tr> <td></td> <td></td> <td></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Fatigue</td> </tr> <tr> <td></td> <td></td> <td></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Feeling swollen</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Family Problems</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Fevers</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Dealing with 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Appendix. 2 Distress thermometer and Problem list – NCCN, adapted Bulgarian version

<p>Моля, първо оградете числото (0-10), което най-добре описва степента на дистрес, която сте изпитали през изминалата седмица, включително днес.</p>	<p>Второ, моля посочете дали някое от следните е представлявало проблем за Вас през изминалата седмица, включително днес. Отбележете ДА или НЕ за всяко.</p>	
<p>Висок дистрес</p> <div style="text-align: center; margin: 10px 0;">  </div> <p>Няма дистрес</p>	<p>ДА НЕ</p> <p>Практически проблеми</p> <p><input type="checkbox"/> <input type="checkbox"/> Грижи за деца</p> <p><input type="checkbox"/> <input type="checkbox"/> Домакинска работа</p> <p><input type="checkbox"/> <input type="checkbox"/> Застраховки/финансови</p> <p><input type="checkbox"/> <input type="checkbox"/> Транспортиране</p> <p><input type="checkbox"/> <input type="checkbox"/> Работа/училище</p> <p><input type="checkbox"/> <input type="checkbox"/> Семейни проблеми</p> <p><input type="checkbox"/> <input type="checkbox"/> Взаимоотношения с деца</p> <p><input type="checkbox"/> <input type="checkbox"/> Взаимоотношения с партньора</p> <p><input type="checkbox"/> <input type="checkbox"/> Взаимоотношения с близки приятели/роднини</p> <p><input type="checkbox"/> <input type="checkbox"/> Емоционални проблеми</p> <p><input type="checkbox"/> <input type="checkbox"/> Депресия</p> <p><input type="checkbox"/> <input type="checkbox"/> Страхове</p> <p><input type="checkbox"/> <input type="checkbox"/> Нервност</p> <p><input type="checkbox"/> <input type="checkbox"/> Тъга</p> <p><input type="checkbox"/> <input type="checkbox"/> Тревожност</p> <p><input type="checkbox"/> <input type="checkbox"/> Загуба на интерес към обичайни дейности</p> <p><input type="checkbox"/> <input type="checkbox"/> Духовни/религиозни притеснения</p>	<p>ДА НЕ</p> <p>Физически проблеми</p> <p><input type="checkbox"/> <input type="checkbox"/> Външен вид</p> <p><input type="checkbox"/> <input type="checkbox"/> Къпане/преобличане</p> <p><input type="checkbox"/> <input type="checkbox"/> Дишане</p> <p><input type="checkbox"/> <input type="checkbox"/> Промяна в уринирането</p> <p><input type="checkbox"/> <input type="checkbox"/> Запек</p> <p><input type="checkbox"/> <input type="checkbox"/> Диария</p> <p><input type="checkbox"/> <input type="checkbox"/> Хранене</p> <p><input type="checkbox"/> <input type="checkbox"/> Умора</p> <p><input type="checkbox"/> <input type="checkbox"/> Усещане за подутост</p> <p><input type="checkbox"/> <input type="checkbox"/> Висока температура/треска</p> <p><input type="checkbox"/> <input type="checkbox"/> Разходки</p> <p><input type="checkbox"/> <input type="checkbox"/> Храносмилане</p> <p><input type="checkbox"/> <input type="checkbox"/> Памет/концентрация</p> <p><input type="checkbox"/> <input type="checkbox"/> Болки в устата</p> <p><input type="checkbox"/> <input type="checkbox"/> Гадене</p> <p><input type="checkbox"/> <input type="checkbox"/> Сух/запушен нос</p> <p><input type="checkbox"/> <input type="checkbox"/> Болка</p> <p><input type="checkbox"/> <input type="checkbox"/> Сексуални проблеми</p> <p><input type="checkbox"/> <input type="checkbox"/> Суха, сърбяща кожа</p> <p><input type="checkbox"/> <input type="checkbox"/> Проблеми със съня</p> <p><input type="checkbox"/> <input type="checkbox"/> Изтръпване в ръцете/краката</p> <p><u>Други проблеми</u></p> <hr style="border: 0.5px solid black;"/>

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