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Comparative analysis between screenings of the levels of distress, anxiety, depression, anger and need for help in patients with solid tumours and pending chemotherapy

SUMMARY

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Abbreviations

In Bulgarian:

ЦНС - Централна Нервна Система

ДНК - Дезокси- рибонуклеинова киселина

ГТР - Генерализирано тревожно разстройство

СТР - Социално тревожно разстройство

ОКР - Обсесивно компулсивното разстройство

In English:

ICCTF – International Cancer and Cognition Task Force

DSMIV - Diagnostic and Statistical Manual of Mental Disorders

TNM – International tumour staging system

PS - Performance status - Standardised criteria for quantification of how the disease affects the patient's everyday abilities

ECOG – A scale from 1 to 5 assessing the performance status

INTRODUCTION

Malignant tumours are widely spread pathological processes that have a high relative share in human pathology. After the containment of a number of infectious diseases, due to their successful treatment with antibacterial agents, cardiovascular diseases and malignant tumours have remained the major problems in medicine and the most common cause of death. According to World Health Organisation statistics, tumours rank second in the overall mortality structure of economically developed countries – accounting for 15 to 22% of the deaths, yielding precedence only to cardiovascular diseases. The medical literature informs of constant, progressive increase in the frequency of occurrence of malignant tumours. However, such an increase has a somewhat relative nature. It can be explained with the longer life expectancy, with the greater healthcare coverage of the population, and in this connection – the more complete registration of the diagnosed and the deaths from malignant tumours. Nevertheless, the increase in the frequency of malignant neoplasms and the growth in the relative share of tumour pathology are indisputable. According to the statistics, about 4.3 million people in the world die of and about 6.3 million people develop malignant neoplasms worldwide each year. The frequencies of the diagnosed and the deaths from malignant

tumours differ as a large number of the diagnosed are treated successfully. However, this ratio between diagnosed and deceased patients is very different for the various neoplasm localisations and forms. For instance, squamous and basal cell carcinoma of the skin are common tumours, but normally they are treated successfully and their mortality rate is actually zero. In recent years, colorectal carcinoma and the carcinoma of the mammary gland and many other localisations have also changed their survival rate due to the introduction of new methods and standards of treatment. The standardised mortality rate in men in Bulgaria is higher than the average for Europe (231.7 per 100,000 and 222.6 per 100,000, respectively), in women it is lower (126.3 per 100,000 and 128.8 per 100,000, respectively). The five-year survival rate in patients with malignant diseases in Bulgaria is lower than the average for Europe – 39.7% and 54.2%, respectively.

Experts define distress as a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioural, emotional) social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis.

All patients experience certain distress related to the diagnosis of cancer, the impact the disease has, and its treatment, irrespective of the stage of the disease. Distress may arise from the reaction after the diagnosis of cancer and the different periods during the course of the disease. Clinically significant stress levels are observed in part of the patients, and distress identification and treatment is of utmost importance. On a global scale, few countries (and also a small number of centres in them) implement distress screening on a routine basis by using validated screening instrument. A survey of 1,000 oncologists in the USA showed that less than a third of them (32.3%) are familiar with the NCCN guidelines on distress screening, and only 14.3% actually conduct screening using a validated instrument for this. In the UK, only 10% of 226 physicians and nurses used a validated screening instrument. A Canadian survey reports that 36.5% of the medical practitioners conducted routine distress screening. There is no summarised information for Eastern Europe and Bulgaria. The barriers to conducting routine screening have been identified as: insufficient time, non-systematic use, a lack of follow-up resources and a lack of commitment on the part of the practitioners who come into contact with the patient.

The presence of mental distress in the different individuals varies depending on the cancer type and stage, as well as on the age, sex and race. The patients with increased risk of moderate or

severe distress are those with a medical history of a psychiatric disorder, depression, substance abuse, and those with a cognitive impairment, severe comorbid diseases, uncontrolled symptoms, communication barriers or social issues. The risk factors include younger age, female sex, living single, young children and past physical or sexual abuse. Learning about a genetic- and family-based risk of an oncological disease is also connected with distress. The early distress assessment and screening lead to early and timely management of psychological distress, which in turn improves the conservative treatment.

The words “psychological”, “psychiatric” and “emotional” are stigmatising, like the word “cancer”. The word “distress” is less stigmatising and is more acceptable to both patients and oncologists than these terms, but the psychological issues remain stigmatised even in the context of battling cancer. Consequently, patients often hide from their doctors information about their distress, and doctors do not ask their patients about their psychological problems. Identifying patients with distress has become more difficult as oncological care is focused on ambulatory check-ups, which are often brief and rushed. Such barriers prevent distress from receiving the necessary attention, despite the fact that distress management is a critical element of the overall care of the cancer patient.

The distress thermometer is used as a rough questionnaire instrument for screening, which identifies distress coming from a random source, and which may even be unrelated to cancer. The receptionist can give it to the patient in the waiting room. Developed by NCCN, now it is a well-known instrument for initial screening, which is similar to the successful pain measurement scale: from 0 (no distress) to 10 (extreme distress). The word “distress” was chosen, as described above, since it is less stigmatising and is more acceptable to the patients and the oncologists than other terms such as psychiatric, psychosocial or emotional. The use of this non-stigmatising word diminishes the clinicians’ apprehensions that the patient will be embarrassed or offended by these questions. Asking an objective question such as “On a scale from 0 to 10, how would you rate your pain today?” makes it easier for and helps the service staff to learn about the patients’ pain. Similarly, asking the question “On a scale from 0 to 10, how would you rate your distress today?” starts a dialogue with the oncologist or about the emotions, whichever is more acceptable.

The patient gives a rating according to the distress thermometer scale in response to the following question: “On a scale from 0 to 10, how would you rate your distress in the last week?” A score of 4 or higher suggests a level of distress of clinical importance: If the patient’s distress level is mild (a score <4 according to the distress thermometer), the primary oncological

team may choose to manage the problems with the usual palliative clinical care. In case the level of patient's distress is 4 or higher, a member of the oncological team reviews the problem list (see below) in order to identify the key problems and asks additional questions to identify the best resources (mental health, social work and consulting, professional chaplains) and to help the patient overcome their worries.

The problem list requires from patients to state their problems in five different categories - practical, family, emotional, spiritual/religious and physical. The team makes a note that the problem list may be modified to meet the needs of the local populace. An analysis of the distress thermometer and the problem list, including an analysis of the main component, the logistic regression and the classification and the regression analyses show the approval of the elements of the Problem list related to emotions (e.g. sadness, anxiety, depression, fear, nervousness, sleep), physical function; (e.g. mobility, taking a bath, dressing, breathing, tiredness, walk, memory/concentration, pain) and support (e.g. spiritual/religious problems, insurance/finances, relationship with the partner), are connected to a large extent with moderate or severe stress ($P < 001$, $P = 003$, $P = 013$).

Primary check-up – it is recommended that prior to the clinical examinations all patients be assessed using a simple screening instrument. As there are several types of screening instruments, it is recommended that the level of stress and the reasons be identified using a Distress Thermometer (DT) and the enclosed problem list. In the event that the patient's distress is moderate or severe (thermometer value ≥ 4), the team of oncologists should take into consideration this prerequisite for referral to the second level of questions, including clinical observations and/or approved schemes/stress and depression tracking. A proper observation may lead to the referral to a mental health specialist, social worker or a chaplain, depending on the problems stated in the problem list. The general symptoms which require additional assessment are: excessive anxiety and fears, excessive sadness, irrational thinking, despair and hopelessness, serious family problems, social problems and spiritual and religious interests. All unresolved physical symptoms should be treated in accordance with the specificity of the disease.

Psychosocial interventions are effective in reducing distress and improving the quality of life of cancer patients as a whole.

The examination studies the various interventions (psychological, social and pharmacological) and their impact on every aspect of the quality of life, the symptoms or the survival. The

comprehensive examination comprises various clinical tests, systematic check-ups and meta-analyses supporting the conclusion that the psychosocial aspects should be included in the everyday care for a cancer treatment. The last meta-analyses have led to similar conclusions, despite the objective need for more tests.

The psychosocial care is increasingly being accepted as an integral part of the clinical services for cancer patients. The treatment of distress in cancer is in aid of the patients, their families, the service staff and the medical staff, and helps towards improving the effectiveness of the clinical services. For cancer patients, the introduction of mental, healthcare and medical services is vital. Spiritualism and religion also play a major part for a number of cancer patients in coping with the diagnose and the disease.

Anxiety

Anxiety is a mental disorder. It is characterised as persistent worry and an irrational feeling of threat, which leads to the feeling of constant fear and insecurity. Patients suffering from anxiety disorder find it beyond their control and it can fully paralyse their activity, involving them in complete inertness and isolation. This makes the disease a very dangerous one, as it visibly impacts the quality of life.

Reasons for the anxiety disorder

The main reason for the occurrence of the anxiety disorder is the stress in our everyday life – in the family or working environment. Stressful situations are part of almost everyone's life, but the people who fail to cope with them develop anxiety. Different traumatic events can also trigger this condition. For example, the death of a close person, the loss of home, a divorce or dismissal.

Genetic predisposition also proves to be a factor in the development of the disorder, as it has been established that patients whose parents suffered from anxiety are more predisposed to

having their mental balance upset. A reason for the occurrence of the disease can also be the biological susceptibility to worry and anxiety.

High sensitivity is connected with the reaction of the organism during the release of adrenaline when the necessary number of neurotransmitters – molecules transmitting information to the central nervous system – is insufficient. Then the necessary balance is not reached and the feeling of fear and worry increases more than it is normal. Several studies have proved how emotions can influence the outcome of the disease. Some authors believe that the presence of anxiety is a surrogate of significant levels of distress. Our results, analogously to other studies, have shown that patients with high levels of distress have a higher risk of developing insomnia and a significant pain syndrome.

Anxiety Disorder Symptoms

The typical symptoms of anxiety include irrational fear, panic attacks, high irritability, poor concentration, worry and constant tenseness. These symptoms have different degrees of manifestation in different people.

In addition to their manifestation on a mental level, the symptoms of the anxiety disorder also occur in a physical aspect through rapid heartbeat, sweating, high blood pressure, headache, rapid breathing, dry mouth, dizziness and muscle tension.

Such symptoms may occur simultaneously, and sometimes in a combination. Untreated anxiety is often the first step to developing depression. Moreover, people suffering from this anxiety disorder are more susceptible to alcohol and drug addiction.

Types of anxiety disorder

- Generalised anxiety disorder (GAD) – this anxiety is characterised by a long period of gnawing anxiety and heavy stress caused by a specific event. A specific event, most often related to the future, makes the people suffering from the disease see the worst possible development of what they expect. The generalised anxiety disorder is diagnosed based on the

uncontrollable anxiety and stress when it comes to the event that is significant to them. In a physical aspect, the symptoms are manifested through dry mouth, sticky hands, dizziness and heavy sweating.

- Panic disorder – while the Generalised Anxiety Disorder is a long-term condition, in panic disorder the attacks last for no more than 10 minutes. In it, anxiety is manifested most often in women, who feel tightness in the throat area, as if choked. The panic also leads to headache, nausea, and rapid heartbeat. The panic attacks are not connected with a specific event and occur suddenly. They are unexpected, and their intense symptoms on a physical level make the patients believe they are dying.

- Social anxiety disorder (SAD) – this disorder involves the occurrence of overwhelming and intrusive fear of social situations. Sufferers experience intense worry that they will be humiliated by the people to whom they speak. It is characterised by disturbances in communication and illogical anxiety with regard to other people's opinion. This condition predominantly occurs in the childhood or adolescence of shy individuals. In the milder cases it is described as a stage fright, and in the more severe ones it leads to complete social isolation.

- Phobias – phobias are an exaggerated fear of a specific object, activity or situations in which there is almost no danger. The most common phobias are of animals such as snakes and spiders, of a confined space (claustrophobia), of heights (acrophobia), and of travelling by plane (pterygophobia). They are characterised by occurrence of intense panic and sufferers from the disease believe that death awaits them if they go near the object of their phobia.

- Obsessive-compulsive disorder (OCD) – it involves appearance of intrusive thoughts that cause intense anxiety and worry. In this disorder, the patient aims to control their fears by performing certain rituals, which they believe will protect them from a certain fatal event.

Terminologically, such rituals are known as compulsions and are manifested by overly frequent washing of the hands, a manic need for certain order in space or ritual counting of a certain action, for example 3 times switching the lighting on and off before going to sleep. Obsessive-compulsive disorder manifests as early as the early childhood and unlike the other anxiety disorders, it cannot be treated. It is possible, however, to relieve the condition of severe anxiety.

- Post-traumatic stress disorder – this is anxiety occurring after exposure to a traumatic event – rape, natural disaster, war incident, death of a relative, sexual or physical abuse. In post-traumatic stress disorder, patients feel complete helplessness and constant terror. Intrusive thoughts that the event will repeat itself occur, and this makes them see danger everywhere without it actually existing. Frequent nightmares about what happened are also a characteristic symptom.

Diagnosis and treatment of the anxiety disorder

The anxiety disorder can be diagnosed only by a doctor who performs a complete examination of the patient's physical and mental condition. After establishing the reason and the type of the anxiety disorder, a treatment plan is prescribed, which often includes therapy with a psychologist, medications and application of relaxation techniques. A key point for the successful treatment is the support of their families. To overcome the disorder, the patient needs to feel the unconditional love of the family and friends.

Validated anxiety scales.

When assessing the need for psychosocial and medical care for an adult oncological patient, it is recommended to carry out monitoring when giving a diagnosis, at regular equal intervals. The anxiety assessment scales may be multimodal and include pharmacological and/or non-pharmacological approaches.

* Beck Anxiety Inventory, BAI. It comprises 21 elements and is completed by the patient for measuring the severity of the somatic symptoms of anxiety. BAI score > 10 is a sign of mild anxiety, while a score > 19 — moderate anxiety. The area of study of the method includes somatic symptoms of autonomous agitation and panic (e.g. rapid heartbeat, sweaty palms). The instrument was developed to differentiate the symptoms of anxiety from the symptoms of depression.

* Generalised Anxiety Disorder Questionnaire-IV, GAD-Q-IV. This is a self-report scale comprising 9 elements, completed to assess symptoms of Generalised Anxiety Disorder, in accordance with the definition of DSM-IV.8. The area of study of the method includes uncontrolled worry, functioning disorder, physical symptoms and subjective distress.

* Generalised Anxiety Disorder-7 algorithm. This is an instrument for clinical interview and assessing anxiety in adult oncological patients. In this algorithm, the word *anxiety* refers to results under GAD-7, and not to a clinical diagnosis of anxiety disorder: (1) initial diagnosis - beginning of the treatment, regular interviews during the treatment, 3, 6 and 12 months after the treatment, diagnosis of recurrence or progression, in the period prior to death and in periods of personal transition or transvaluation, such as a family crisis; (2) presence of the symptom in the past two weeks (0 = never, 1 = several days, 2 = more than half the days, and 3 = almost every day)

Depression

Generally, depression is a feeling of melancholy, sadness, despair, helplessness and despondency, which may last from several hours to several days. If a long-term feeling of sadness and despair is present, this may be the case of a disorder known as major depressive disorder.

Depression can be provoked by various factors – biological, mental and social (such as birth, bereavement, divorce, learning about a serious diagnosis – e.g. cancer). We have all felt sad, helpless or dissatisfied at some point in our life. For most of us, these feelings are an entirely normal response to stressful or unpleasant events, such as financial hardships or the end of a romantic affair. The negative feelings can be painful and excruciating, but they pass and become less intense with the passage of time.

When your mood is extremely sad or negative on most days and worsens or becomes more intense in time, you may have an affective disorder. The affective disorder is a serious change of or disturbance in the mood which provokes the individual to experience extreme or excruciating emotions and affects their ability to function normally. The major depressive disorder, or depression, is one of the commonest affective disorders in the USA and leads to extreme, constant feelings such as sadness and hopelessness, which may have a weakening effect on the individual's physical and mental health.

The brain works continuously to help one respond to the experienced. To do that, it relies on chemical messengers called neurotransmitters. Neurotransmitters are powerful instruments for

communication which help the various areas of the brain to control most bodily functions, including behavioural processes such as sleep and appetite, and emotional processes such as mood and concentration. Neurotransmitters interact with goals in the brain so that one can respond to situations in an appropriate and healthy manner.

Sometimes, they stop working properly and cause problems in the communication system of the brain. A situation called chemical disbalance may change various aspects of the mental and the physical health. Many scientists believe that the severe behavioural and emotional changes in the depression are caused by a disbalance or dysfunction of neurotransmitters called monoamines. Monoamines are found in great concentrations in the limbic system of the cerebrum, which controls the emotions, sleep, appetite and memory. When the monoamine concentration is too low, symptoms of depression appear.

Main symptoms

A feeling of complete despair, hopelessness, and pointlessness of everything. Persisting sadness and depression. A feeling of anxiety and helplessness. A feeling of emptiness. Anger and irritability. A feeling of guilt. Loss of confidence. A lack of interest in the everyday activities, indifference. A lack of motivation. Chronic fatigue, a lack of energy, lethargy. Difficult concentration, memory disorders. Difficult decision-making, passivity. Inability to feel pleasure. Fear about the future. Suicidal thoughts or suicide attempts. Eating disorders: loss of appetite – weight reduction, increase in appetite – gaining weight. Sleep disorders: difficulty falling asleep (insomnia, early waking), a feeling of tiredness after a sleep of normal duration.

About 5% of adults in the world and 6.9% of adults in the USA face depression at some point in their lives. There is a greater chance to experience depression if one is female, suffers from a disease such as cancer or heart condition, and lives in a region with poor accessibility to treatment services and jobs. The spreading of the depression has made suicide a significant problem for public healthcare in the USA and in 2013 it was 10th leading cause of death. The share of suicide is especially high among the vulnerable groups of the population, such as war veterans, people identifying themselves as lesbians, gays, bisexual, transsexual and young people aged 15 to 24.

Clinical interviews for assessment of depressiveness.

All patients should undergo depressiveness screening upon their initial visit to the oncologist, and after that at certain intervals or when necessary. It is especially important that this happen in the transition to palliative care. The special circumstances in the assessment of depressiveness include the following: the patient's cultural characteristics, cognitive abilities, recognition of the fact that depression is difficult to identify in elderly oncological patients.

The oncological patients with depression have misgivings about their disease - 70%, about the relationships with their friends - 77%, about the welfare of their family - 74%, and about their finances - 63%.

Above all, depression is connected with an increased risk of death – relative risk 1.22-1.39 and risk of oncological disease relative risk 1.18. Two clinical studies have validated the higher risk of suicide in patients with longer survival rate and breast or testicular cancer.

The following depression assessment scales have been validated:

* Beck Depression Inventory, BDI. One of the reliable depression tests is the Beck Depression Inventory. Devised in 1961, today Beck's test is considered one of the most professional questionnaires, allowing for reliable identification of the level of depression. In the development of this test, Aaron Beck relied on the clinical observations of depressive patients. After a few years of clinical observation, he identified the most common symptoms of various types of disorders.

The original version of this test offers a special scale with 21 signs of depressive conditions. All these conditions are ranked according to the level of the manifestations, so Beck's scale not only allows for establishing the presence of a depressive condition, but also for identifying the degree of its severity. In addition, Beck's original depression test includes two subscales: the scale of somatic manifestation of the depressive condition (score 14-21) and the affective-cognitive scale (score 1-13). These subtests allow for rather reliable identification of the type of depression. The diagnostic conclusion is based on the results of the subjective assessment of their condition of the very subject. They themselves work with the test, providing a score from

0 to 3 opposite each function (question). Following the completion of the form, the therapist counts the total score and then compares the results with the suggested test interpretation. The total score varies from about 0 to 63, and the higher the result, the more severe the condition of the specific person manifesting this mental disorder is.

*Nashtop Rating Scale for Depression. The method comprises 7 elements and is applied to assess the severity of the symptoms of depression, in accordance with the definition of DSM-IV. A score of 7-17 under HAM-D indicates mild depression, 18-24 – moderate depression, and a score > 25 is a sign of severe depression. The area of study of the instrument includes depressive mood, insomnia, agitation, anxiety and weight loss.

*Patient Health Questionnaire for Depression, PHQ-9. The scale comprises 9 elements and is self-reported by the patient to assess the symptoms of a major depressive disorder, according to the definition of DSM-IV. The area of study of the method covers depressive symptoms and concomitant functionality disorder. More than half of the patients with oncological diseases manage well, demonstrating remarkable mental toughness on being given the diagnosis, during the treatment and afterwards. Even when the psychological reactions during active treatment are satisfactory, a subgroup of patients remains vulnerable to later manifestations of distress. Irrespective of the moment and the circumstances in which concomitant psychiatric disorders occur, if the anxiety disorders and the depression are not treated this may have enormous emotional, interpersonal and financial repercussions for the patients, as well as economic impact for the health service provider and the healthcare system.

*Centre for Epidemiological Studies Depression Scale (CES-D, CES-D-SF). The self-reported questionnaires comprise 20 or 10 elements. A score higher than 16 is a sign of moderate to severe depression. These scales are relatively independent of the presence of physical symptoms.

*Hamilton Depression Rating Scale (PHQ-9) – The method consists of 17 questions. According to the DSM-IV definition, a score of 7-17 suggests mild depression, 18-24 moderate depression, and a score higher than 24 is indicative of severe depression.

Anger

Anger is defined as part of the generalised anxiety disorders and an emotional disorder. Emotions make people behave in a way which, from the evolutionary theory perspective, protects them from a threat, causes them to new social relationships, encourage them in various activities, bringing satisfaction and urging them to explore the environment. Anger is an emotion connected with the individual's psychological interpretation for an insult, injustice to their personality and a tendency to react vengefully.

When we get angry, the heart rate, arterial tension and testosterone production increases, cortisol (the stress hormone) decreases, and the left hemisphere of the brain becomes more stimulated. This was established by a group of scientists from the University of Valencia, who analysed the changes in the brain's cardiovascular, hormonal and asymmetric activation response when we get angry. "Inducing emotions generates profound changes in the autonomous nervous system, which controls the cardiovascular response, and also in the endocrine system. In addition, changes in cerebral activity also occur, especially in the frontal and temporal lobes," Neus Herrero, main author of the study). The researchers induced anger in 30 men using the version that has been adapted to Spanish of the procedure "Anger Induction" (AI), consisting of 50 phrases in first person that reflect daily situations that provoke anger. Before and immediately after the inducement of anger they measured the heart rate and arterial tension, the levels of testosterone and cortisol, and the asymmetric activation of the brain, the general state of mind and the subjective experience of the anger emotion. Emotions (including anger) are of transitory nature. They come and go. Managing anger equals gaining command of the bodily symptoms of anger through the mind. It is about the individual allowing themselves enough time to respond to their feelings, asking the right questions about their angry reaction, taking the right decision on how to react when they are angry and to decide whether they are willing to face the consequences of their aggressive behaviour.

Ninety per cent of the people do not react immediately after they start feeling angry. The hormone released in our body to negate the stronger effects of adrenaline is called Acetylcholine. In some cases, it is not right for the individual to indulge the belief that emotions should be left to pass. Naturally, anger should pass quickly. For most people, the fit of anger varies from 5 to 10 minutes, but for others it may vary in terms of severity and duration. Anger can be explosive, i.e. directed to external objects, or implosive, i.e. self-directed.

Explosive anger finds an expression in aggressive actions, accusations, insults, communication “for increased moral or other pressure”, et. Implosive anger translates into self-criticism, feeling guilty, depression, self-harm, self-isolation, etc. One type of anger can convert into the other, and a mixture of the two types of anger can also be seen – for instance, feeling insulted when a person becomes angry at another individual and at the same time at themselves, as if they “swallow” the original anger. the clash of the two types of anger may result in a nervous breakdown.

Normally, it is a rare occasion for therapists to have their services sought for anger management, but in the course of treatment of another problem anger often comes to the fore as a dominating emotion that determines other symptoms. Anger, malice, hatred or insult may take possession of the individual, causing depression, relationship disruption, isolation, anxiety, a number of psychosomatic symptoms, even psychoses. Anger and hatred are chronic emotions experienced by patients who have very serious diagnoses, and in them the intensity of these feelings is strikingly high. Nevertheless, even normal, completely healthy people, who sometimes suffer from excess anger, do not know how to manage with that and carry out actions they will later regret, harm themselves, spoil other people’s mood, and sometimes even ruin their own lives. Anger should not be confused with aggression: anger is an emotion, and aggression is behaviour. Anger, however, often provokes the individual to commit aggression. It, as an emotion, is an element of the motivational core of the personality. For this reason, the literature on the topic of aggression the emotion of anger is covered to a large extent.

Anger, as stated above, has predominantly defensive functions. It helps in situations where one has difficulties. If such situations are extraordinary, when anger is actually the only way to overcome dissatisfaction, then it is necessary and justified, although an alternative solution can be found in almost every situation. In the cases when a person manifests anger that is unnecessary a suspicion arises that they have no skills for normal and confident solving of the problems. Consequently, some part of their personality feels helpless when facing certain difficulties. It is that part precisely that produces anger to compensate for its inadequacy.

Need for help

This psychological category is extremely hard to interpret and assess. There are no validated questionnaires, definitions and manuals for it. Especially for oncological patients. This is due to the fact that it is a matter of a strictly individual expression of a mental attitude and a mixture of a multitude of feelings and symptoms related to the oncological disease. The patients find it rather difficult to understand by themselves when and to what extent they need help. “The physician knows that just as there is sickness which is only imaginary, so also there is such a thing as fictitious health. In the latter case, therefore, the physician first employs medicines to cause the disease to become manifest ... So it is also with the physician of souls when dealing with despair. He knows what despair is, he is acquainted with it, and hence he is not satisfied with a man’s assertion that he is in despair or that he is not...” - Søren Kierkegaard (1813 — 1855). It is hardly necessary to convince anyone of the need for psychological help in oncology. Authoritative research points out develop the entire range of psychiatric disorders. According to Holland (1992), the subject matter of psycho-oncology is the emotional reactions of the patients, of the members of their family and of the individuals helping the patients. The concept of “quality of life” was first developed for the patients with oncological profile, but when it is time to do something specific, the psychological needs of the patients and their physicians are ignored.

The need for help arises as early as the stage of announcement of the diagnosis. This happens with no preparation, among other things, and is shocking for the patient. The physician has not organised their time to provide sufficient information and develop a therapeutic plan together with the patient. The model of one-way explanations, which are in the physician’s competence, dominates, and the patient has to enter into the role of a passive performer. An example in this respect is the following clinical case – six months after cervical conization, a young woman is in depression, experiences panic attacks and is afraid to be left alone. She started coping with these conditions after she stopped hearing the doctor’s voice telling her that if no hysterectomy was performed, she would die! She overcame the crisis with the help of her family. All that time, the woman communicated her need for help. Everyone responds differently to similar news and in a large percentage of the cases they need help.

The diagnostic process is accepted not as a study of the disease, but as a mechanical process of “giving” a diagnosis, in which the physician acts from the position of the expert who knows everything. Alas, each physician knows how few the cases in which this is so are and modern medicine is focusing on the joint therapeutic decision model. In this method, physician and patient both help the healing process; they support each other even in the event of a negative prognosis. This promotes cooperation, recognises the patient’s personality and their efforts to recover, despite the fact that they do not always meet the scientific ideas of the disorder and that their feeling a need for help is reduced considerably.

Although the physician is sensitive to the psychology of the course of the disorder, the conversation about the patient's personal experiences requires skills that exceed the level of spontaneous psychology. This motivates the team's needs for psychological training, burnout prophylaxis training and joint work with an oncological psychiatrist and a psychiatrist. The scientific standards bind the physician to conform to the limits of professional competence and refer the patient to a psychologist for a personality test. Psychological work should not be considered an additional job, but an equivalent part of the treatment. In such conditions it is appropriate to include tranquilisers and antidepressants, psychotherapeutic sessions for confidence maintenance, realistic ideas of the treatment process and the behaviour during the course of the disorder.

Testing 50 patients in an oncological clinic, A. Peck established that most of them had guessed the diagnosis during the preliminary tests; they were well-informed but avoided talking about the problem since it burdened them, and not because they did not realise the disease – that is they deliberately avoided seeking help. Kosta Zaimov observed defensive para-affective reactions, which were expressed through low self-esteem and false smiles. The patient defended themselves from intrusive questions about whether they would recover, how long they were expected to live, and who would take care of the children. According to A. Thostov, patients are well aware that they have cancer and will not live long, they want to be informed about the data from the analyses, to be told “the truth”, they make plans, doubt the test results, seek additional consultations, swing from despair to hope. Their accounts, compared to the control group, are short, indefinite, with several versions, what happens is the result of fate and not because of the circumstances or a specific person.

The very word *cancer* suggests a fatal case with agonizing death. The mental state of the person who has heard they may have cancer for the first time goes through five stages: 1) Denial or shock. 2) Anger. 3) Negotiation. 4) Depression. 5) Acceptance. In the beginning, the individual refuses to believe and has the data checked by other specialists, but during the latent period of shock they may not take any steps. In the second stage, the individual musters their strength and becomes angry at the doctors, the society and the relatives. In the third stage, the patient tries to gain time. In the fourth one, they avoid friends and their pastimes, confining themselves to their home and bemoaning their fate. Eventually, the patient musters their strength to live for their family. The stages do not always follow a certain order. The patient may become stuck in their recovery or return to their previous state. What is important, however, is that going through

all these stages the patient has the feeling of a need for help and expects to receive it from the physician and their family.

Evidently, to adapt to the disorder and conduct the process of recovery in a reasonable manner, the patient has to resolve difficult psychological problems. The first task of the psychotherapy is to help them to believe in the treatment and in the capacity of the organism to overcome the disease. It is especially important that the patient reevaluate the problems prior to the disorder and believe they can make effective decisions. This new attitude gives hope for the future and supports the recovery process.

Aim of the dissertation

The aim of this dissertation paper is to conduct screening and identification of distress and the psychoemotional categories depression, anxiety, anger and a need for help and their correlational dependency in oncological patients with pending first chemotherapy through application of validated emotion thermometers.

To achieve this aim, we set the following objectives:

- To screen patients diagnosed with an oncological disease and identify the levels of distress, depression, anxiety, a feeling of anger and a need for help by employing the respective emotion thermometers.
- To establish a correlation between the factors sex, age, type of the oncological disease, stage of the oncological disease, performance status and the levels of the aforementioned psychoemotional states.
- To identify the risk factors for presence of high levels of distress, depression, anger, and a need for help
- To determine the internal consistency of the employed thermometers

Based on the studied literature and the set aim of the dissertation study, the following hypotheses have been formulated:

It is possible to facilitate the identification of the patients with distress and mental disorders by determining in advance high-risk groups, which will be given priority when screening.

Except by the standard factors sex, age, and stage of the disease, the patients can also be stratified by factors that are characteristic of a given nation, ethnicity or religion, which will provide an opportunity to identify and interpret distress in greater detail.

Design of the dissertation study

Design of the experiment:

Subject of the study: The study includes at least 225 patients with proven oncological disease and referred for treatment to the Medical Oncology Clinic at St. Marina UMHAT.

The following emotion thermometers will be studied – distress, anxiety, depression, anger and a need for help – for stratification of the patients by sex, age, ethnicity, religion, education, income, etc. The information about additional stratification by clinical and pathological characteristics of the oncological disease (surgery, type of the surgery, type of the oncological disease, histology, TNM stage, etc.) will be collected from the available medical documentation.

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Inclusion criteria:

- Individuals over 18 years of age
- Histologically confirmed oncological disease
- Patients of the Medical Oncology Clinic at St. Marina UMHAT

- Patients beginning the first course of neoadjuvant, adjuvant or first-line chemotherapy

Exclusion criteria:

- Individuals identified as endangered populations (youngsters under 18 years of age, pregnant women, prisoners, socially disadvantaged people)

- Unproven oncological disease

- Patients of other institutions

- performance status 2 or 3

- Individuals who cannot assist in the study

Dissertation paper stages:

- Literature overview and analysis of the problems related to distress, depression, anxiety, anger and a need for help
- Exit distress assessment
- Assessment of the other thermometers and their correlation with distress
- Statistical processing of the results,
- Interpretation of the results.

Research methods

Historical method – study of literature sources.

Documentary method:

A. International screening programmes

B. Programmes and manuals for screening and action in cases of distress in effect in Bulgaria at present

Methods of medical and statistical data processing:

Planned methods of statistical data processing and result interpretation:

1. Method of statistical grouping of the data – categorization of the symptoms according to their type in variational, interval, category, exponential and dynamic statistical rows.

2. Graphical method – use of linear and planar graphic images, pie charts, stereograms and symbol charts.

3. Nonparametric analyses – for assessment of the categorical indicators - criterion χ^2 (chi-squared) as per Pearson. For the comparisons by sex and age groups - Mann-Whitney and Kruskal-Wallis non-parametric tests.

4. Correlation analysis – for identification of single-variable coefficients of a Spearman's linear correlation. $Rho < 0.19$ – very weak correlation, $Rho = 0.19-0.39$ – weak correlation, $Rho = 0.40-0.59$ – moderate correlation, $Rho = 0.60-0.79$ – strong correlation, $Rho > 0.8$ – very strong correlation

5. Multiple-partial correlation analysis, where the assessment of the correlation between two variables takes into account the influence of other factors, e.g. sex, age, etc.

6. Regression analysis – In regression analysis, the dependencies are taken into account as follows: a dependent variable (effect) and several factors (independent variables);

According to the number of the factors: single-factor; two-factor; multiple-factor. According to the type of the dependencies: linear – linear dependencies; non-linear – any type of non-linear dependencies.

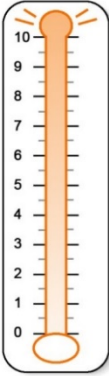
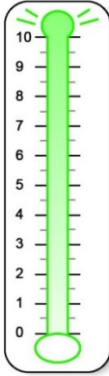
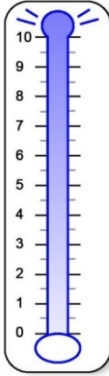
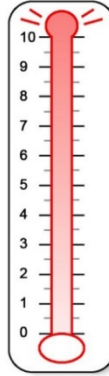
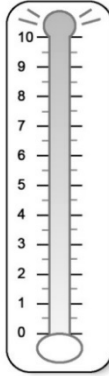
7. Cronbach's alpha (α) was used as an objective rater of the reliability of the employed thermometers. Values over 0.80 are accepted as a good indicator of internal consistency.

Research Instruments

Questionnaire card – a validated questionnaire with a distress thermometer – a standard NCCN instrument with additional information – social and demographic data. The questionnaire includes five thermometers assessing (through self-report) the level of distress, anxiety, depression, anger and the need for help (as per a visual analogue scale from 0 to 10, which is a line calibrated from 0 to 10. Zero (0) indicates the lowest level of the studied problem, and ten (10) – the highest. The patients reporting thermometer values ≥ 4 were deemed patients with high levels of distress, anxiety, depression, anger and a need for help by analogy with the validated distress thermometer.

Emotion Thermometers 5 items

Instructions
In the first four columns, please mark the number (0-10) that best describes how much emotional upset you have been experiencing in the past week, including today.
In the last column please indicate how much you need help for these concerns.

	1. Distress	2. Anxiety	3. Depression	4. Anger	5. Need Help	
Extreme						Desperately
None						Can manage by myself

Adapted from the NCCN Distress Thermometer. Alex J Mitchell © 2012

Emotion thermometers

Results and discussion

1. Demographic and clinical and pathological characteristics of the study participants

A non-interventional scientific study was conducted. The study covered the period 2016-2017 (with follow-up to 2018), and included 225 surveyed patients who met the inclusion criteria.

Patients' basic characteristics:

The descriptive analysis of the information about the patients (social and demographic and clinical and pathological) established that the average age of the patients is 59.6 +/- 11.4, with minimum age of 29 years, and maximum age 81 years.

The distribution of the individuals by sex shows that the women are 126 (56%), and the men are 99 (44%) (Table 1).

The surveyed patients are in a good general condition, which is assessed using the ECOG scale – performance status (PS). Depending on PS, patients with assessed PS-1 dominate by a narrow margin - 122 (54.2%), as compared to those with PS-0 - 103 (45.8%). All 225 patients participating in the study have a histologically confirmed oncological diagnosis in stage II, III and IV. When analysing the collected data, we established a minimum difference between the respondents in II/III non-metastatic stage 104 (46.2%) and IV metastatic stage 121 (53.8%). (Table 1)

Men	Women	PS 0	PS 1	II and III stage	IV stage
99 (44%)	126 (56%)	103 (45.8%)	122 (54.2%)	104 (46.2%)	121 (53.8%)

Table (1) Distribution of the patients by clinical and pathological characteristics (number, %)

In the general group of the surveyed patients, the lowest percentage is that of the singles 17 (7.6%), divorced 21 (9.3%), and widowed 28 (12.4%), followed by the married 159 (70.7%). The analysis of the family status of all surveyed patients shows that the married ones are 159

(70.7%), the single ones – 17 (7.6%), the divorced – 21 (9.3%), and the widowed – 28 (12.4%). (Table2)

Family status			
Single	Married	Widowed	Divorced
17 (7.6%)	159 (70.7%)	28 (12.4%)	21 (9.3%)

Table (2) Distribution of the patients according to their family status (number, %)

From the distribution by ethnicity we established that the group of the respondents of Bulgarian origin consists of 209 patients (92.9%), and that of Turkish origin – of 16 (7.1%). (Table 3)

Ethnicity	
Bulgarian	Turkish
209 (92.9%)	16 (7.1%)

Table (3) Distribution of the patients according to their ethnicity (number, %).

Based on the processed data, we established that according to the professed religion the Christians are 147 (65.3%), the Muslim – 14 (6.2%), and the atheists – 38 (16.9%). 26 (11.6%) of the surveyed patients could not identify with any religion. (Table 4)

Religion			
Atheist	Christian	Muslim	Unspecified
38 (16.9%)	147 (65.3%)	14 (6.2%)	26 (11.6%)

Table (4) Distribution of the patients according to the religion professed by them (number, %).

The analysis of the results shows that the patients with secondary education are 123 (54.7%), those with tertiary – 57 (25.3%) and 45 (2%) of the studied group have primary education. (Table 5)

Education		
Primary	Secondary	Tertiary
45 (2%)	123 (54.7%)	57 (25.3%)

Table(5) Distribution of the patients according to their educational and qualification level (number, %).

This study included and surveyed 225 patients with a histologically confirmed oncological disease, of which 53 (23.6%) with lung carcinoma, 59 (26.2%) with breast cancer and 60 (26.7%) with colorectal carcinoma. All other localisations (large intestine, prostate, rectum, urinary bladder, ovary, cervix, uterus, testicle, stomach, head and neck, pancreas, extragonadal germ cell, parotid gland, retroperitoneal sarcoma, pleural mesothelioma, oesophagus, urethra, tonsil, peritoneum, bile ducts) account for 53 (23.6%) of the total number of the respondents (Table 6).

Localisation	
Lung	53 (23.6%)
Breast cancer	59 (26.2%)
Colorectal carcinoma	60 (26.6%)
Other (over 14 different localisations)	53 (23.6%)

Table (6) Distribution of the patients according to the tumour localisation (number, %).

Analysis of the results of the measured levels of distress

The analysis of the results of the measured level of distress shows that the individuals with low level of distress are 114 (50.7%), and those measuring a moderate/high level of distress – 111 (49.3%). (Table 7)

Level na distress	
Low <4	114 (50.7%)
Moderate/high \geq 4	111 (49.3%)

Table (7) Distribution of the patients according to the level of distress measured with the distress thermometer (number, %).

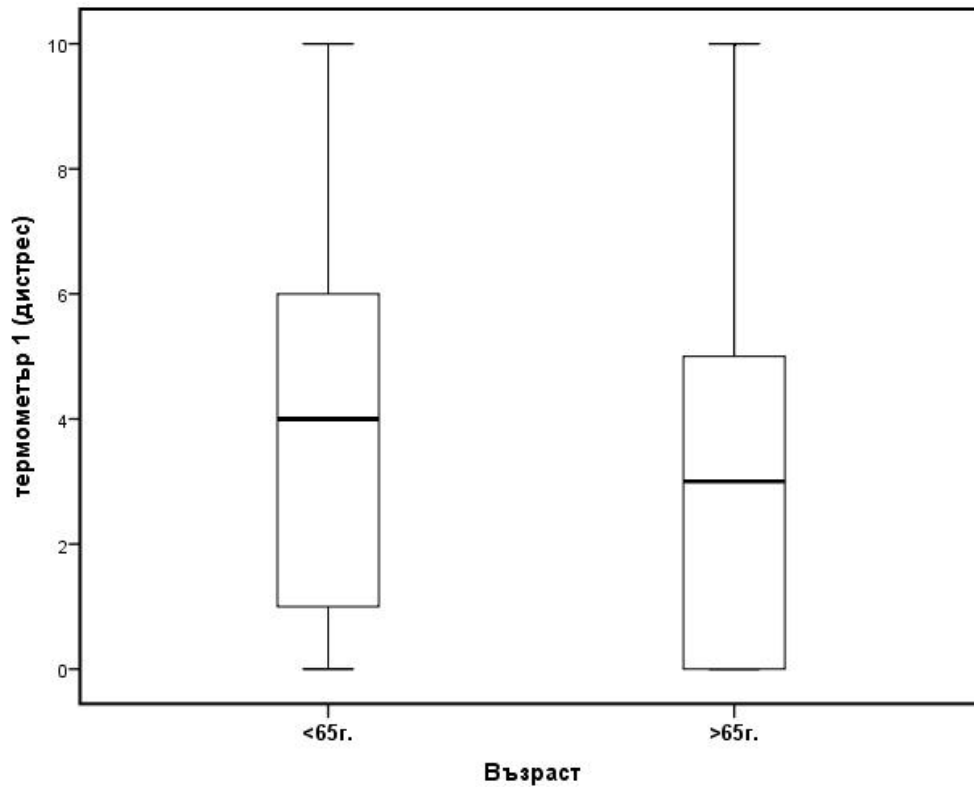
The Chi square analysis of the sociodemographic data shows that there is no dependency between the characteristics age, sex, religion, ethnicity and residence (remoteness from the oncological centre) and the level of distress measured with the Distress thermometer. There is a correlation between the performance status, carcinoma localisation, level of education and the level of distress. (Table 8)

Distress thermometer			
Age	Low level of distress	Moderate/high level of distress	P value
\leq 65	64	72	0.13
>65	50	39	
Sex			
Men	55	45	0.3
Women	60	65	
Stage			
II and III	54	52	0.7
IV	61	58	
PS			0.006
0	66	47	
1	46	66	
Residence (remoteness)			0.7
Varna	64	65	
outside Varna	50	46	
Religion			0.1
Atheist	23	15	
Christian	68	79	
Muslim	6	8	
Unspecified	17	9	

Ethnicity			0.2
Bulgarian	108	101	
Turkish	6	10	
Education			0.017
Primary/Secondary	92	75	
Tertiary	22	36	
Localisations			0.001
Lung	17	36	
Breast cancer	27	32	
Colorectal carcinoma	34	36	
Other (over 14 different localisations)	35	18	

Table (8) Correlation between the sociodemographic and the clinical and pathological characteristics and the level of distress in patients.

In the analysis of the collected data we established that the larger part of the patients are below 65 years of age – 137 (60.9%), and those above 65 years of age – 88 (39.1%). We established that in the patients below 65 years (4.07 ± 3.07) there is a tendency towards higher levels of distress than in those above 65 years of age (3.39 ± 3.08) ($p=0.08$). (Figure 2)



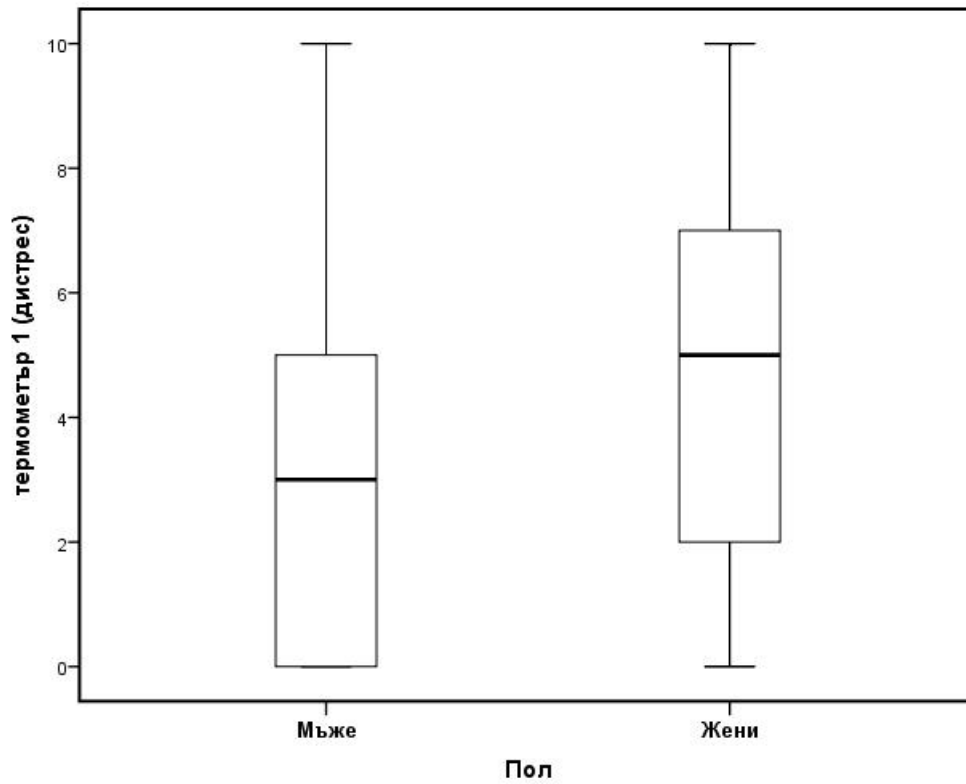
thermometer 1 (distress)

< 65 y.o. 65 y.o.>

Age

Figure (2). A Boxplot illustrating the levels of distress in patients below 65 years old and above 65 years old. The abscissa shows the age, and the ordinate – the level of distress на the patients. The Mann-Whitney analysis shows that there is a tendency towards a higher level of distress in patients below 65 y.o. (4.07 ± 3.07) compared to the respondents above 65 y.o. (3.39 ± 3.08) ($p=0.08$).

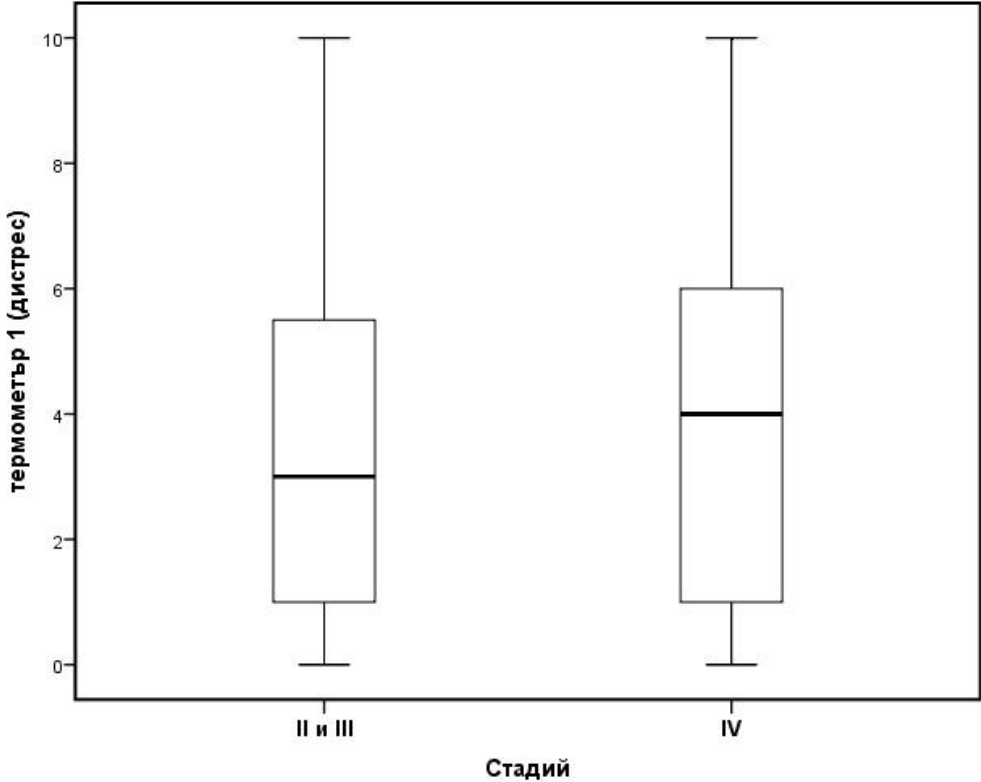
The results of the conducted analysis with regard to the sex of the patients indicate that there is a significantly higher level of distress in the female respondents compared to the male respondents. (Figure 3)



thermometer 1 (distress) Men Women
 Sex

Figure (3). A Boxplot illustrating the levels of distress in male and female patients. The abscissa shows the sex of the patients, and the ordinate – the level of distress. The Mann-Whitney analysis shows that there is a significantly higher level of distress in the female respondents (4.3 ± 3.2), compared to the male respondents (3.2 ± 2.8) ($p=0.014$).

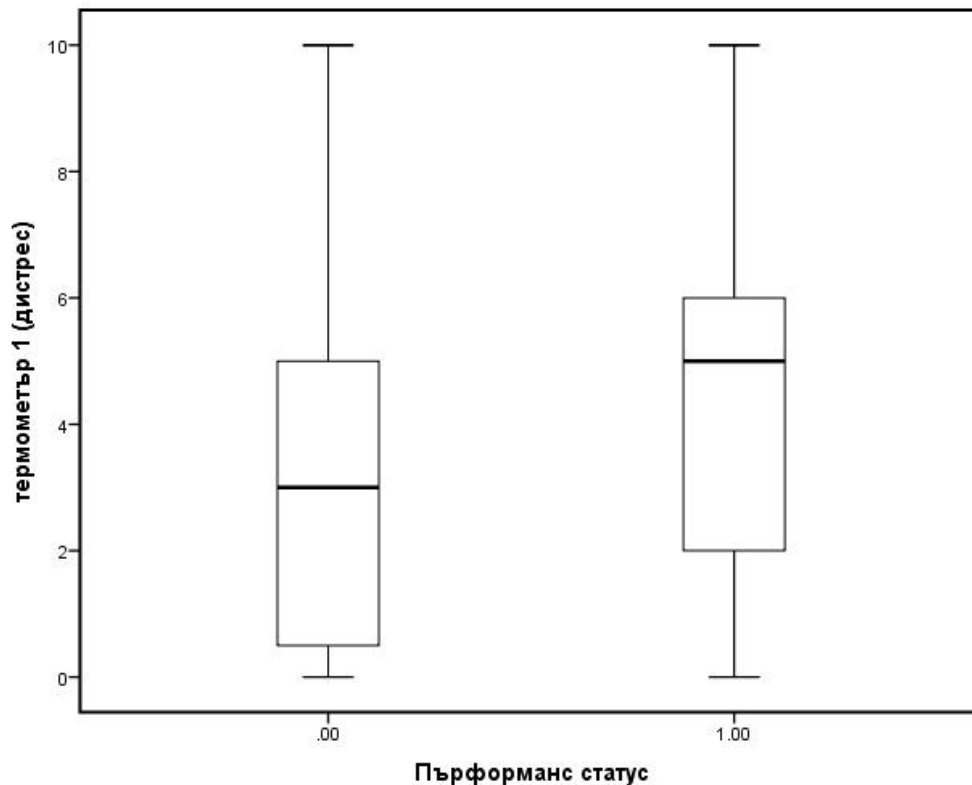
The Mann-Whitney analysis shows that there is no difference in the level of distress in patients with confirmed oncological diagnosis in stage II/III (non-metastatic) (3.6 ± 3.1) and those in stage IV (metastatic stage) (3.9 ± 3.2) ($p > 0.05$) . (Figure 4)



thermometer 1 (distress) II and III IV
Stage

Figure(4). A Boxplot illustrating the level of distress in patients depending on the stage of the disease. The abscissa shows the stage of the disease, and the ordinate - the level of distress of the patients.

The results of the conducted analysis show that there is a significantly higher level of distress in patients assessed using the ECOG scale – performance status 1 (4.4 ± 3.1) compared to those with performance status 0 (3.4 ± 3.2) ($p=0.029$). (Figure 5)

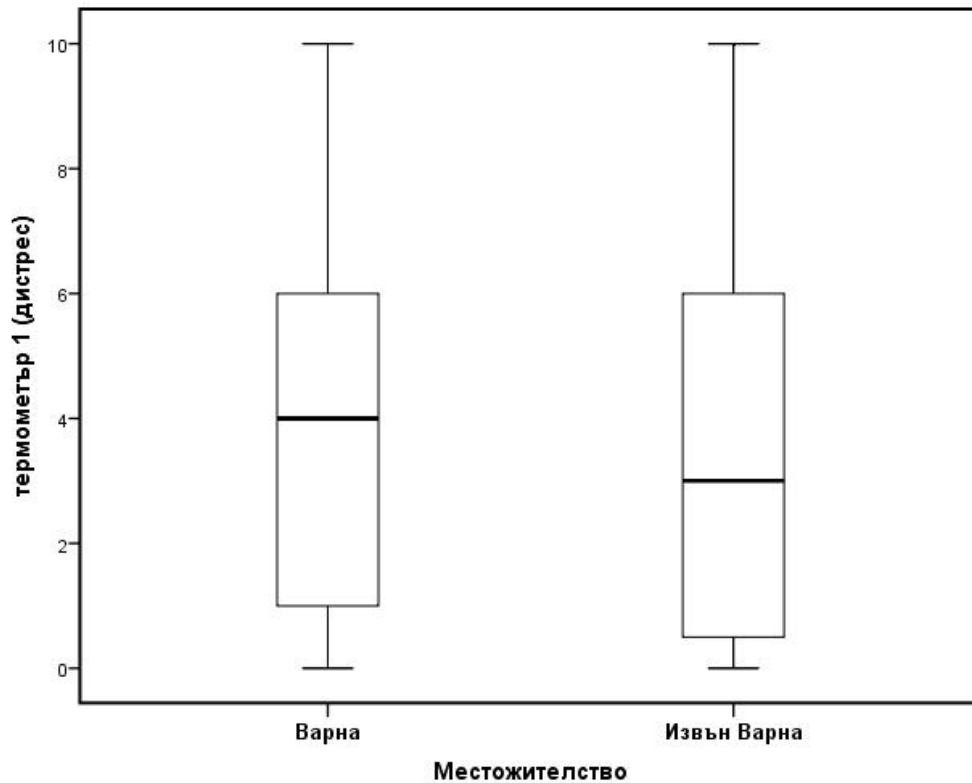


thermometer 1 (distress) Performance status

Figure (5). A boxplot illustrating distribution by general condition of all patients according to the ECOG scale. The abscissa shows the performance status (PS) , and the ordinate - the level of distress of the patients. The Mann-Whitney analysis shows that there is a significantly higher level of distress in patients with PS 1 (4.4 ± 3.1) compared to those with PS 0 (3.4 ± 3.2) ($p=0.029$).

The results of the study show that the majority of the general group live in the city of Varna - 129 (57.3%), and those who do not reside in Varna are 96 (42.7%). We established an

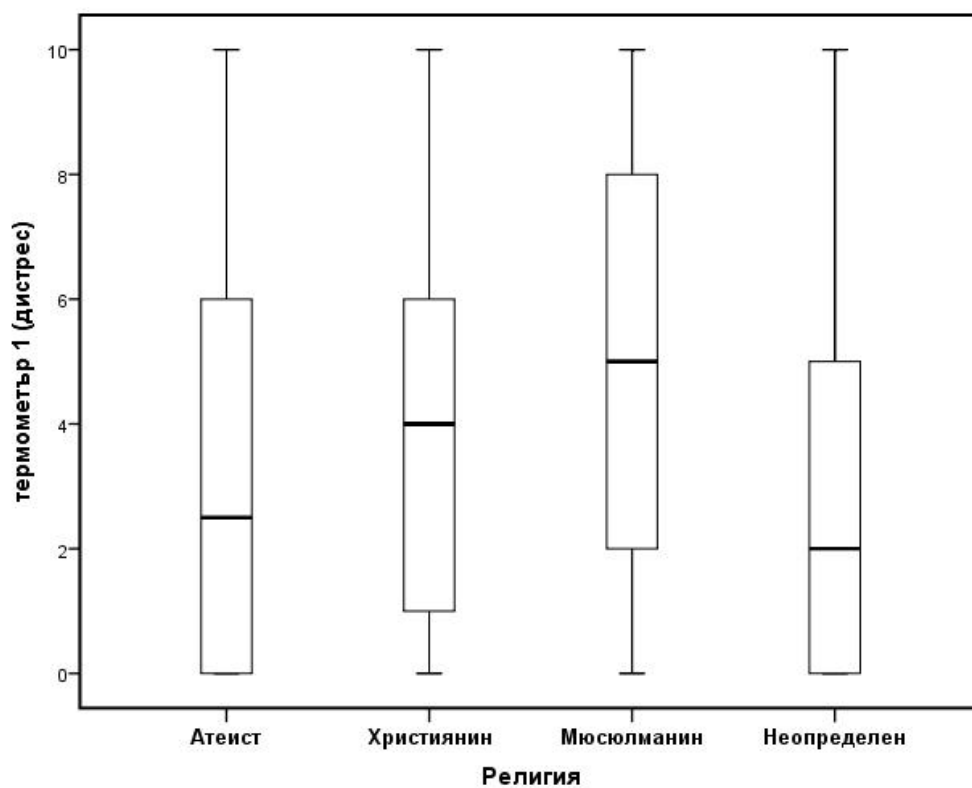
insignificant difference between the level of distress in patients residing in Varna (3.84 ± 3.0) and of the individuals with residence elsewhere (3.76 ± 3.2) ($p > 0,05$). (Figure 6)



thermometer 1 (distress) Varna Outside Varna
Residence

Figure (6). A boxplot illustrating the distribution of the patients by residence. The abscissa shows the place of residence, and the ordinate – the level of distress of the patients. The Mann-Whitney analysis indicates an insignificant difference in the level of distress in patients residing in Varna (3.84 ± 3.0) and those not residing in Varna (3.76 ± 3.2) ($p > 0.05$).

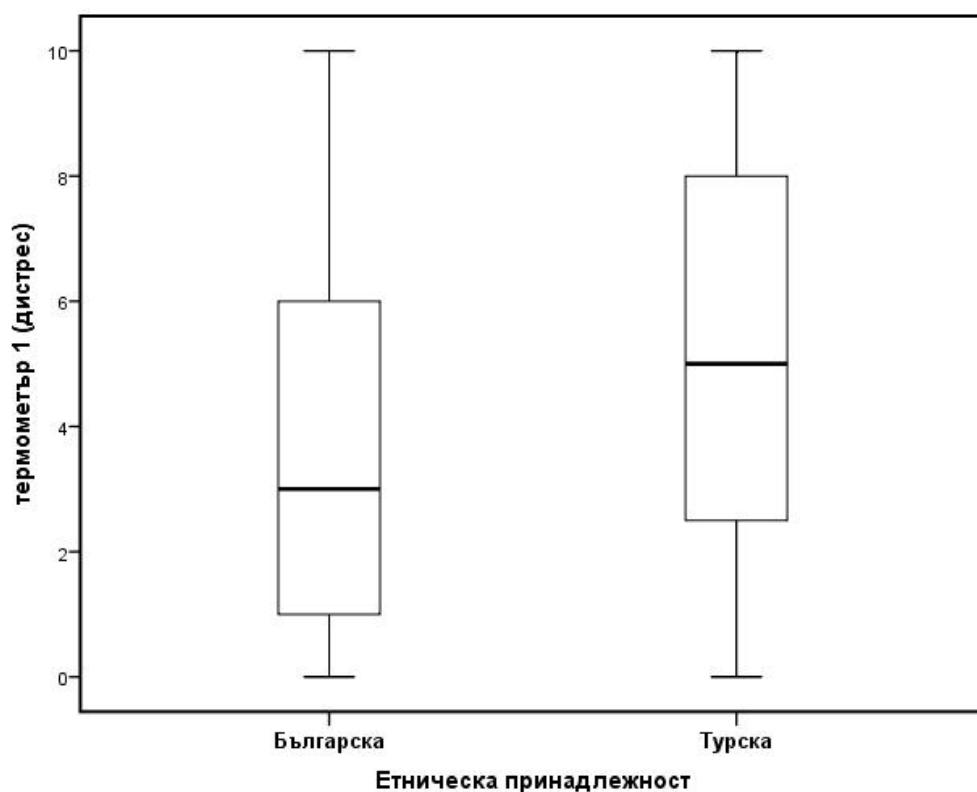
In the general group of patients, the lowest percentage is that of the Muslims – 14 (6.2%), followed by the patients who do not wish to identify their religious affiliation – 26 (11.6%), and the atheists – 38 (16.9%). The largest group is that of the patients who stated Christianity as the religion they profess – 147 (65.3%). The Kruskal-Wallis analysis shows a tendency towards a correlation between the professed religion and the level of distress ($p=0.07$). The patients who do not wish to specify their religion have a level of distress ($2.7\pm.6$), which is lower compared to that of the Christians (4.1 ± 3.1), the Muslims (4.7 ± 3.6) and the atheists (3.05 ± 2.8) . (Figure 7)



thermometer 1 (distress) Atheist Christian Muslim Unspecified
Religion

Figure (7). A boxplot illustrating distribution of the patients by the religion professed by them. The abscissa shows the religion of the patients, divided into four groups, and the ordinate - the level of distress of the patients. The Kruskal-Wallis analysis shows a tendency towards a correlation between the professed religion and the level of distress ($p=0.07$).

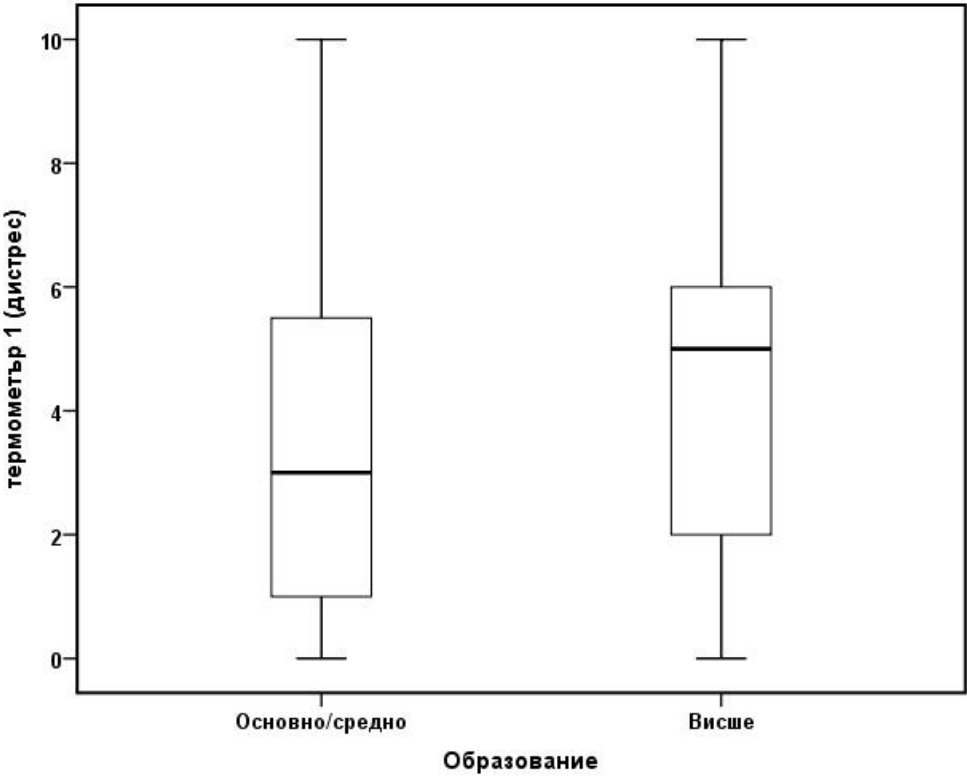
In the analysis of the results, we established that in patients of Turkish ethnicity (5.2 ± 3.4) there is a tendency towards a higher level of distress compared to those of Bulgarian ethnicity (3.7 ± 3.0) ($p=0.08$). (Figure 8)



thermometer 1 (distress) Bulgarian Turkish
 Ethnicity

Figure (8). A boxplot illustrating the levels of distress in patients depending on the ethnicity. The Mann-Whitney analysis shows that there is a tendency towards a higher level of distress in the Turkish ethnicity. The abscissa shows the ethnicity, and the ordinate – the distress in the Turkish ethnicity (5.2 ± 3.4) compared to the respondents of Bulgarian ethnicity (3.7 ± 3.0) ($p=0.08$).

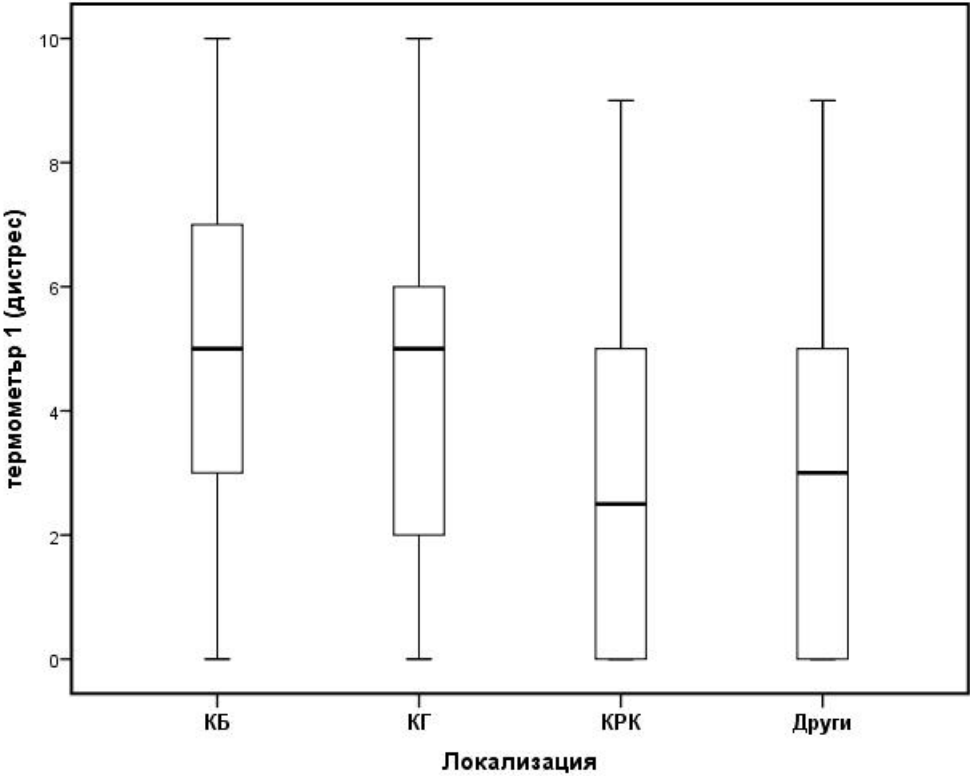
The results of the analysis conducted by us show that in the patients with tertiary education (4.4 ± 2.9) there is a tendency towards a higher level of distress compared to the patients with secondary and primary education (3.6 ± 3.1) ($p=0.017$). (Figure 9)



thermometer 1 (distress) **Primary/Secondary** **Tertiary**
Education

Figure (9). A boxplot showing the distribution of the patients by their level of education and qualification. The abscissa illustrates the level of education, and the ordinate - the level of distress of the patients. The Mann-Whitney analysis shows that there is a tendency towards a higher level of distress in patients with tertiary education (4.4 ± 2.9) compared to those with secondary and primary education (3.6 ± 3.1) ($p=0.017$).

The analysis by localisation shows that the patients with lung carcinoma (4.9 ± 3.1) have a significantly higher level of distress compared to those diagnosed with colorectal carcinoma (3.02 ± 2.7) ($p=0.002$). No significant difference in the level of distress is identified between patients with lung carcinoma (4.9 ± 3.1) and those with breast carcinoma (4.3 ± 3.2). The patients with breast carcinoma (4.3 ± 3.2) have a higher level of distress compared to the patients with colorectal carcinoma (3.02 ± 2.7) ($p=0.018$). (Figure 10)



thermometer 1 (distress) LC BC CRC Other
Localisation

Figure(10). A boxplot illustrating distribution of the patients by the localisation of the primary tumour, distributed in four main groups. The abscissa shows the most common localisations among the respondents – lung carcinoma, breast carcinoma, colorectal carcinoma and other localisations. The ordinate indicates the level of distress of the patients.

The single-factor logistic regression analysis shows that the single individuals, the poor performance status, and the patients with lung and breast carcinoma are associated with a higher risk of high levels of distress – respectively:

single (OR 5.3, 95% CI, 1.2-21.3; p=0.02);

poor performance status (OR 2.14, 95% CI, 1.24-3.7; p=0.006)

lung carcinoma (OR 4.9, 95% CI, 2.1-11.3;p=0.001)

breast carcinoma (OR 2.7 , 95% CI, 1.2-6.1; p= 0.01)

A single-factor regression analysis of the possibility for the given indicator to predict the high levels of distress among the patient population (p-0.044).(Table 9)

	OR	CI 95%	p-value
Sex	0.75	0.44-1.24	0.3
Age	0.66	0.38-1.14	0.1
Stage	0.72	0.6-1.8	0.7
Performance status	2.14	1.24-3.7	0.006
Lung carcinoma	4.9	2.1-11.3	0.001
Breast carcinoma	2.7	1.2-6.1	0.01

Table (9) A single-factor regression analysis of the possibility for the listed factors to predict high levels of distress

The multi-factor regression analysis shows that performance status 1 is associated with presence of high levels of distress (OR 3.09,95% CI 1.5-6.1,p=0.001). The lung carcinoma and the breast carcinoma remain independent predictors of high levels of distress among the patients with OR 6.7, 95% CI 2.5-18.3, p=0.001 and OR 3.4, 95% CI 1.16-10.4, p=0.02. (Table 10)

	OR	CI 95%	p-value
Sex	0.64	0.28-1.45	0.28

Age	1.4	0.72-3.03	
Stage	1.44	0.66-3.1	0.3
Performance status	3.09	1.5-6.1	0.001
Lung carcinoma	6.7	2.5-18.3	0.001
Breast carcinoma	3.4	1.16-10.4	0.02

Table (10) A multi-factor regression analysis of the possibility for the given factors to predict the high levels of distress among the patient population

Analysis of the results of the measured levels of anxiety

A hundred and twenty-seven (56.4%) of the patients reported high levels of anxiety.

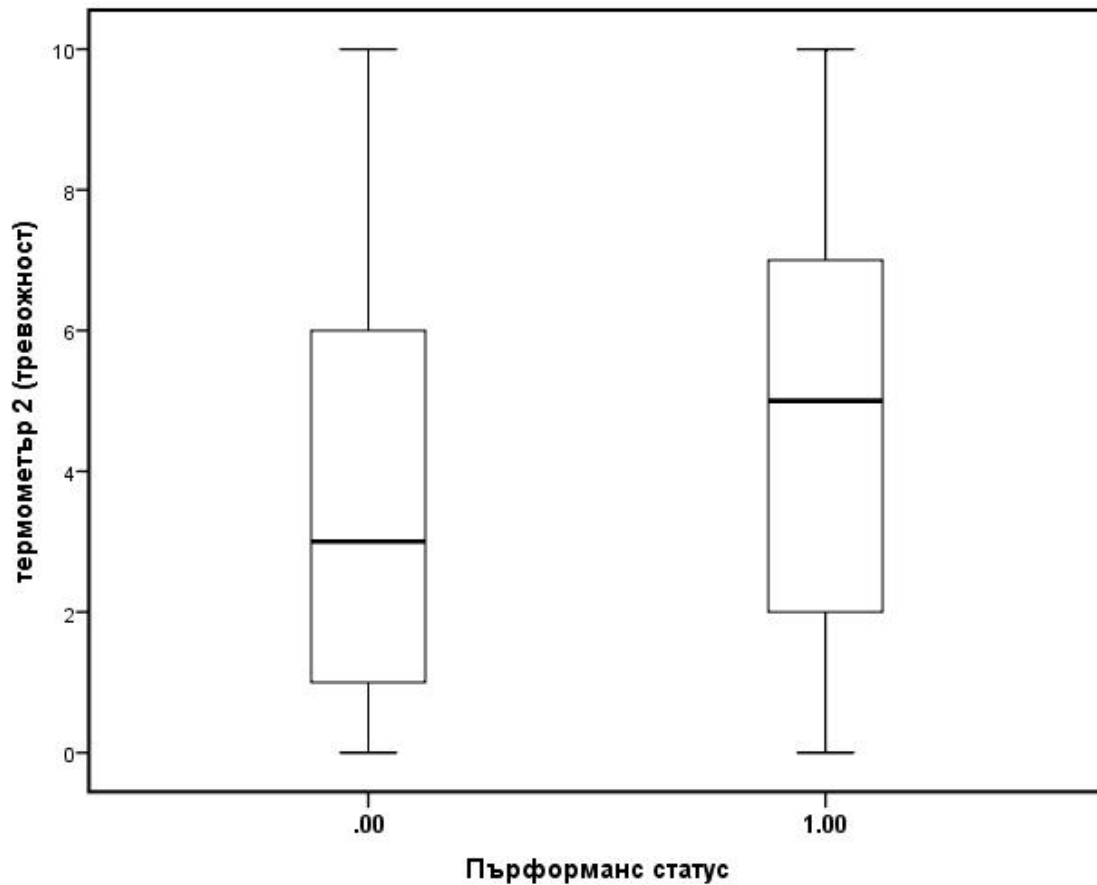
The chi square analysis of the sociodemographic data shows that there is no dependency between the characteristics age, sex, religion, ethnicity and residence (remoteness from the regional oncological centre) and the level of anxiety. A correlation between the performance status, the type of carcinoma and the level of anxiety can be observed. (Table 11)

Anxiety thermometer			
	Low level of anxiety	High levels of anxiety	P value
Age			0.6
≤65	58	79	
>65	40	48	
Sex			0.18
Men	48	51	
Women	50	76	
Stage			0.24
II and III	54	52	

IV	44	75	
Performance status			0.043
0	43	51	
1	55	76	
Localisation			0.009
Lung	16	37	
Breast cancer	20	39	
Colorectal carcinoma	32	28	
Other (over 14 different localisations)	30	23	

Table (11). Dependency between the characteristics age, sex, religion, ethnicity, residence (remoteness from the regional oncological centre), and localisation and the level of anxiety.

The Mann-Whitney analysis shows that there is a significantly higher level of anxiety in patients with PS 1 (4.5 ± 2.9) compared to those with PS 0 (3.56 ± 3.1) ($p=0.043$). (Figure11)

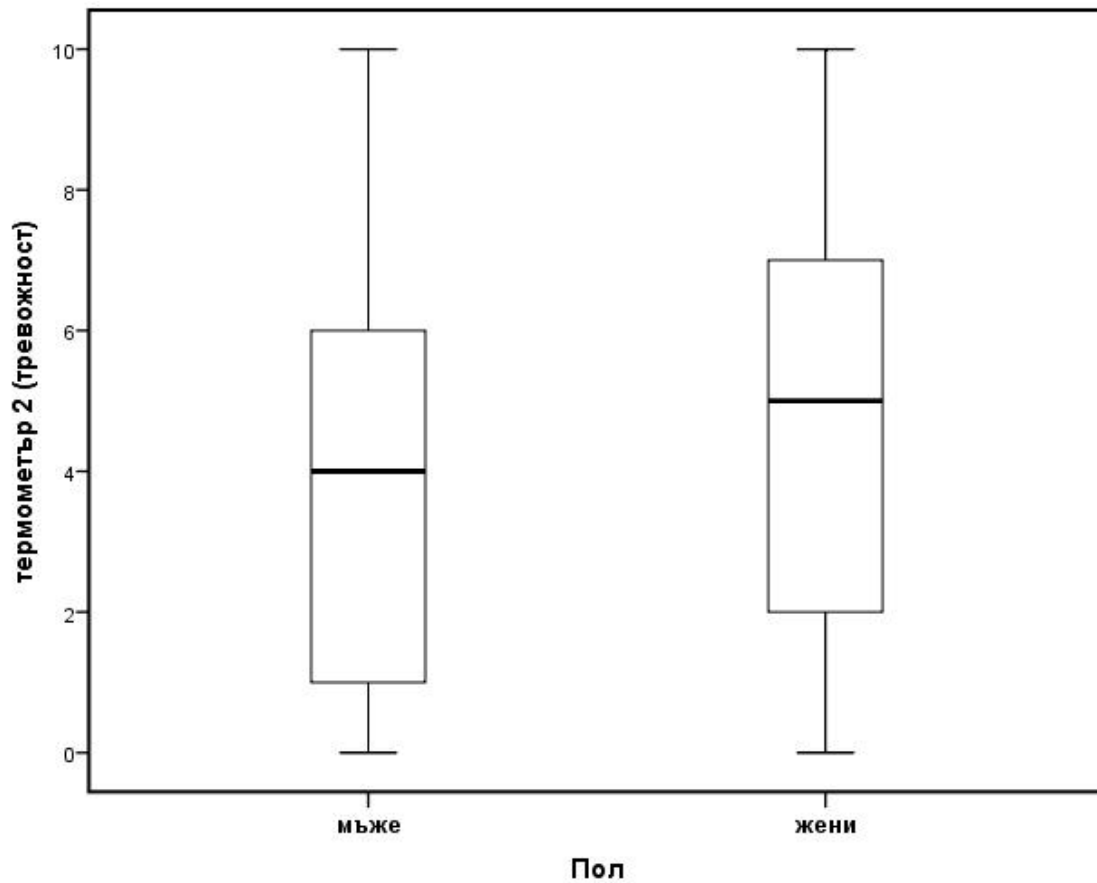


thermometer 2 (anxiety)

Performance status

Figure (11). A boxplot illustrating distribution by the general condition of all patients according to the the ECOG scale. The abscissa shows the performance status (PS) , and the ordinate - the level of anxiety of the patients.

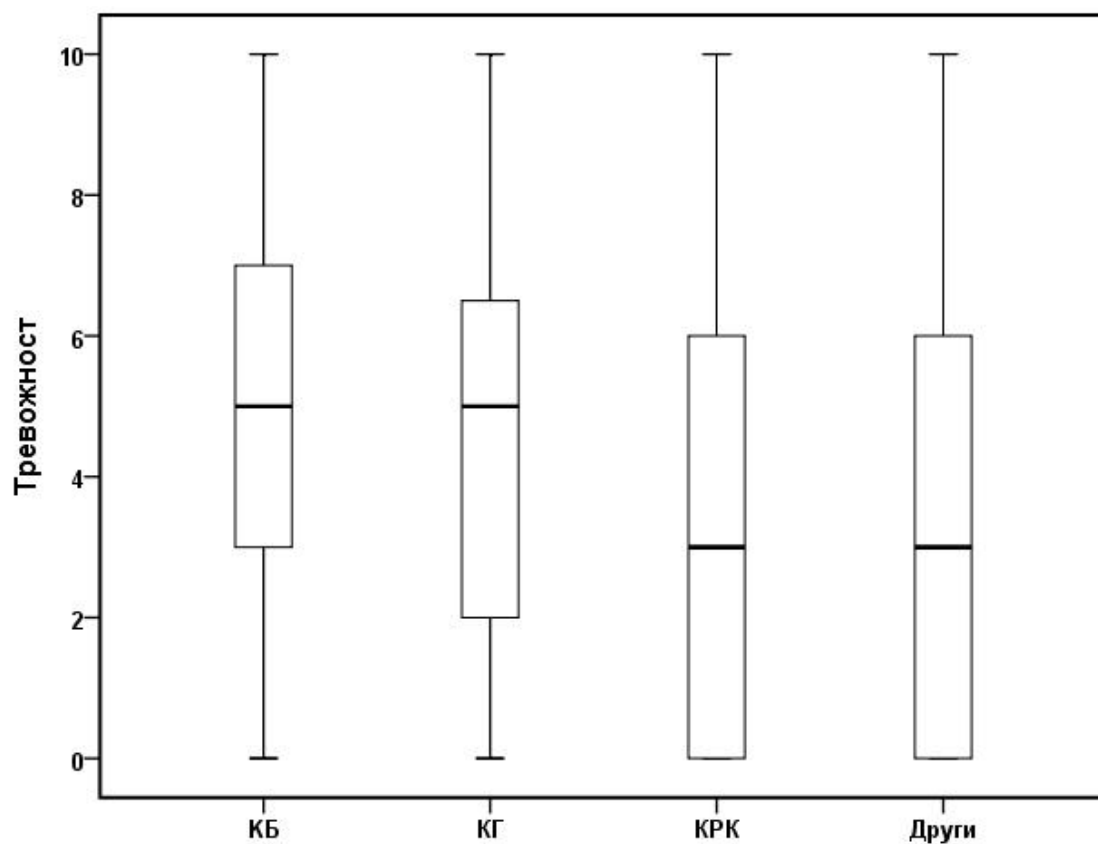
The Mann-Whitney analysis shows that there is a significantly higher level of anxiety in female respondents (4.4 ± 3.1) compared to the male respondents (3.6 ± 2.8) ($p=0.045$). (Figure 12)



thermometer 2 (anxiety) men women
 Sex

Figure (12). A boxplot presenting the levels of anxiety in female and male patients. The abscissa illustrates the sex of the patients, and the ordinate – the level of anxiety.

The conducted Man-Whitney analysis shows significantly higher levels of anxiety in the patients with breast ($p=0.02$) and lung ($p=0.009$) carcinoma compared to patients with colorectal and other type of carcinoma. (Figure 13)



Anxiety

LC BC CRC Other

Figure (13). A boxplot illustrating the distribution of the patients by the localisation of the primary tumour, distributed in four main groups. The abscissa displays the most common localisations among the respondents - lung carcinoma, breast carcinoma, colorectal carcinoma and other localisations. The ordinate shows the level of anxiety of the patients.

An analysis of the possibility for the given factors to predict by the high levels of anxiety among the patient population. In this case, a single-factor regression analysis is used. (Table 12)

	OR	CI 95%	p-value
--	----	--------	---------

Sex	0.69	0.41-1.19	0.18
Single	3.43	1.05-11.2	0.041
Remoteness	1.019	0.59-1.72	0.9
Age	1.13	0.65-1.92	0.6
Stage	0.72	0.42-1.24	0.2
Performance status	1.75	1.016-3.04	0.044
Lung cancer	2.94	1.31-6.61	0.009
Breast cancer	2.48	1.14-5.39	0.02

Table (12) – A single-factor regression analysis of the possibility for the given factors to predict by the high levels of anxiety among the patient population

The following factors are associated with a higher risk of presence of high levels of anxiety:

Singles (CI 95% 1.016-3.04 p=0.044)

Patients with breast carcinoma (CI 95% 1.14-5.39 p=0.02)

Lung cancer (CI 95% 1.31-6.61 p=0.009)

Analysis of the results of the measured levels of depression

Fifty (22.2%) patients reported high levels of depression.

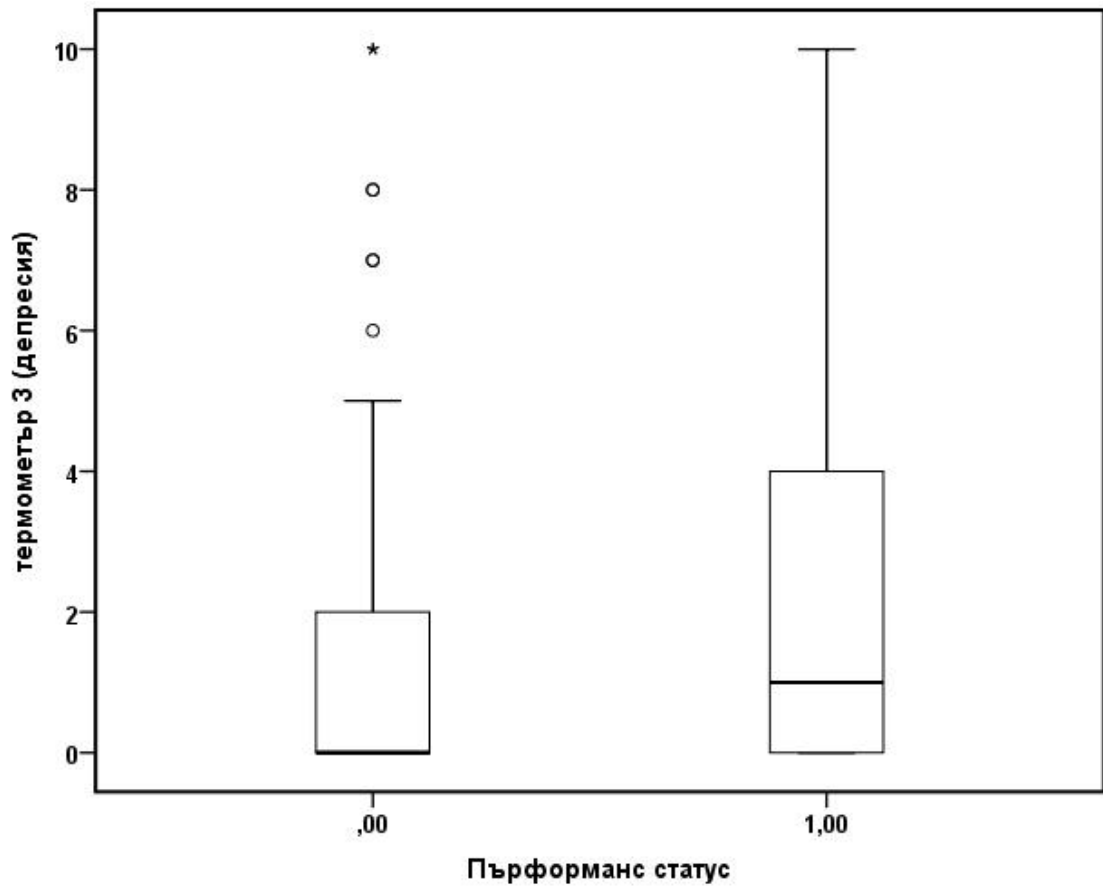
The chi square analysis of the sociodemographic data shows that there is no correlation between the characteristics age, sex, religion, ethnicity and residence (remoteness from the regional oncological centre) and the level of depression, measured with a depression thermometer. A correlation between the performance status, carcinoma localisation, and the level of depression is observed. (Table 13)

Depression thermometer

	Low levels of depression	High levels of depression	P value
Age			0.8
≤65	106	31	
>65	69	19	
Sex			0.7
Men	78	21	
Women	97	29	
Stage			0.7
II and III	82	22	
IV	91	28	
Performance status			0.004
0	79	21	
1	88	39	
Localisation			0.005
Lung	32	21	
Breast cancer	47	12	
Colorectal carcinoma	49	11	
Other (over 14 different localisations)	48	7	

Table (13). Correlation of the characteristics age, sex, religion, ethnicity, and residence (remoteness from the regional oncological centre) and the level of depression.

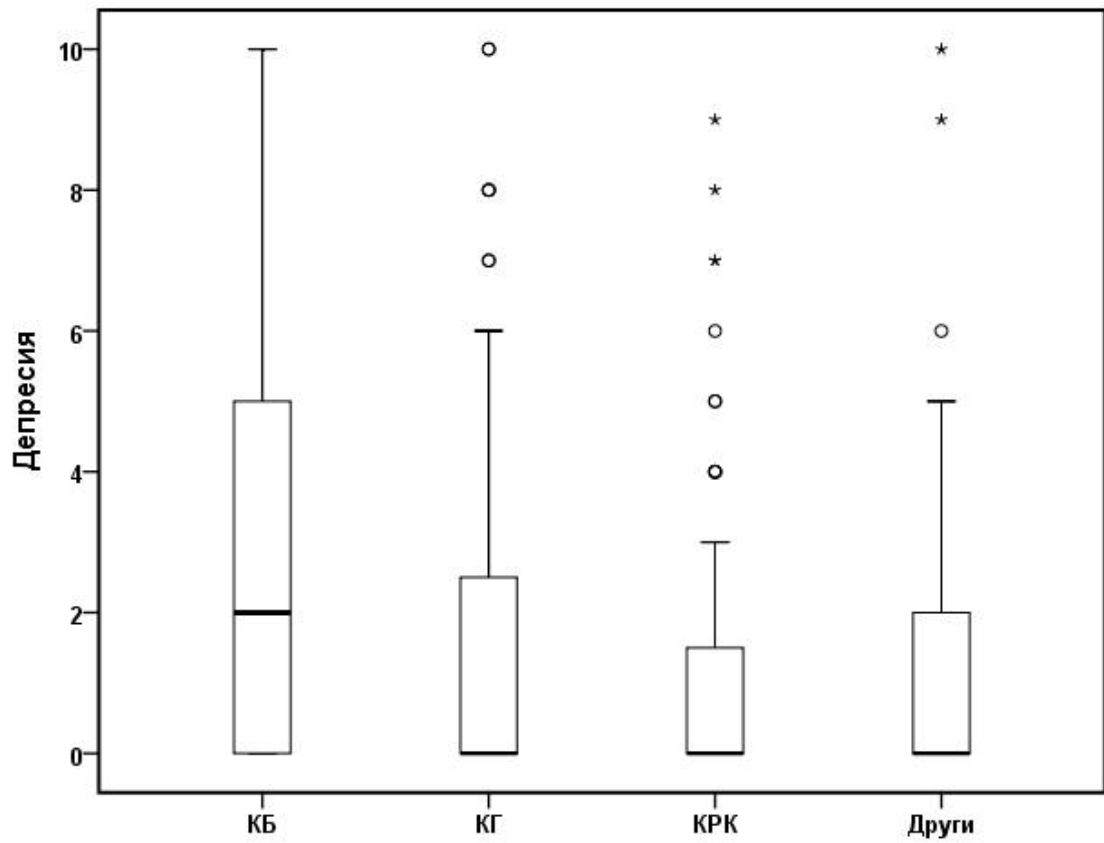
The conducted Mann-Whitney analysis shows a significantly higher level of depression in the patients in a worse Performance status-1 ($p=0.004$) and with carcinoma localisation – lung and mammary gland ($p=0.0005$) (Figures 14 and 15)



thermometer 3 (depression)

Performance status

Figure (14). A boxplot illustrating distribution by the general condition of all patients according to the ECOG scale. The abscissa shows the performance status (PS) , and the ordinate – the level of depression of the patients.



Depression

LC BC CRC Other

Figure (15). A boxplot illustrating the level of depression by localisations of the most common carcinomas. The abscissa shows the most common carcinomas, and the ordinate – the level of depression of the patients.

A single-factor regression analysis of the possibility for the given factors to predict the high levels of depression among the patient population. (Table 15)

	OR	CI 95%	p-value
Sex	0.901	0.477-1.701	0.7
Family status	3.95	0.66-23.7	0.2
Remoteness	1.44	1.03-2.85	0.014
Age	1.06	0.55-2.01	0.8
Stage	0.89	0.43-1.69	0.7
Performance status	2.37	1.19-4.74	0.005
Lung cancer	4.81	1.74-13.2	0.002
Breast cancer	1.87	0.64-5.4	0.2

Table (15). A single-factor regression analysis of the possibility for the given factors to predict by the high levels of depression among the patient population

The following factors are associated with a higher risk of higher levels of depression:

- Remoteness (CI 95% 1.03-2.85) p=0.014
- Performance status (CI 95% 1.19-4.74) p=0.005
- Lung cancer (CI 95% 1.74-13.2) p=0.002

Analysis of the results of the measured levels of anger

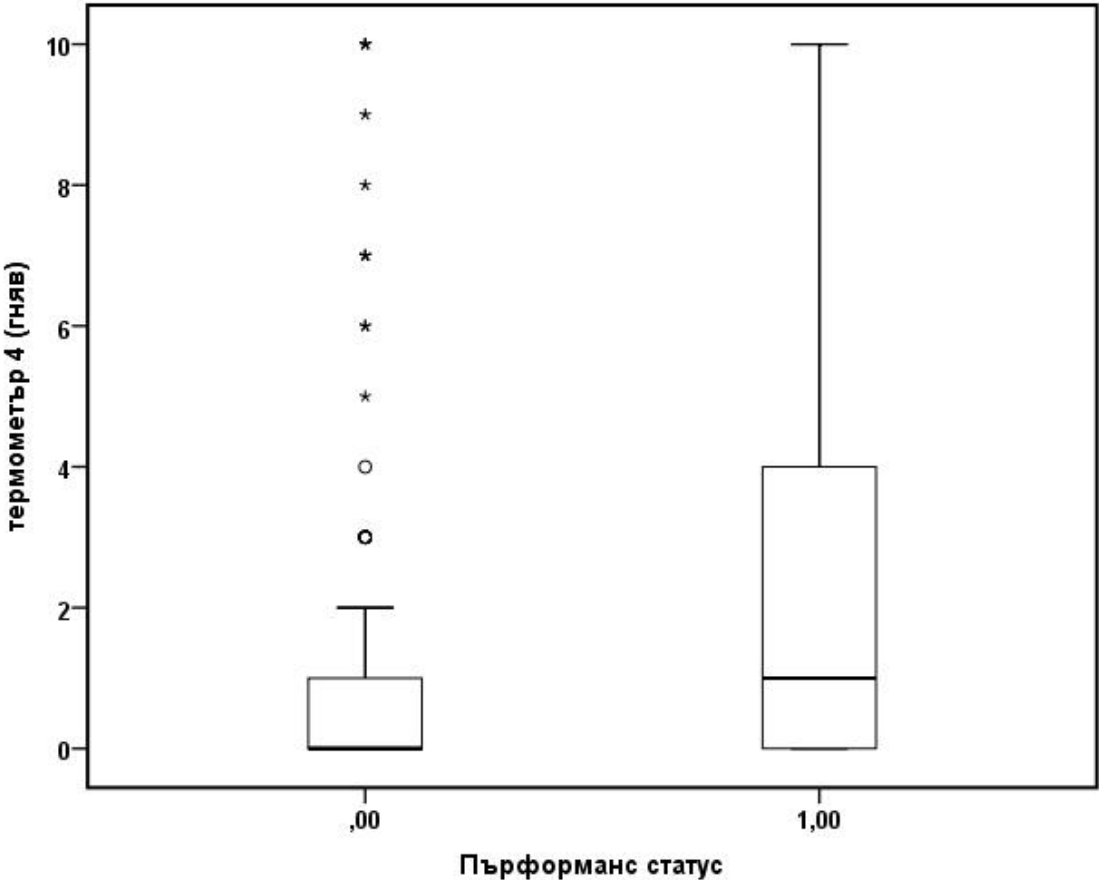
Forty-four (19.6%) patients reported a strong feeling of anger.

The chi square analysis of the sociodemographic data shows that there is no dependency between the characteristics age, sex, religion, ethnicity and residence (remoteness from the regional oncological centre) and the level of the feeling of anger measured with anger thermometers. A correlation between the performance status, carcinoma localisation and the level of the feeling of anger can be observed. (Table 16)

Anger thermometer			
	Low distress	High distress	P value
Age			0.09
≤65	115	22	
>65	66	22	
Sex			0.025
Men	73	26	
Women	108	18	
Stage			0.4
II and III	86	18	
IV	92	25	
Performance status			0.002
0	82	12	
1	92	32	
Localisation			0.015
Lung	35	18	
Breast cancer	53	6	
Colorectal carcinoma	50	10	
Other (over 14 different localisations)	43	10	

Table (16). Sociodemographic data and their correlation with the level of the feeling of anger

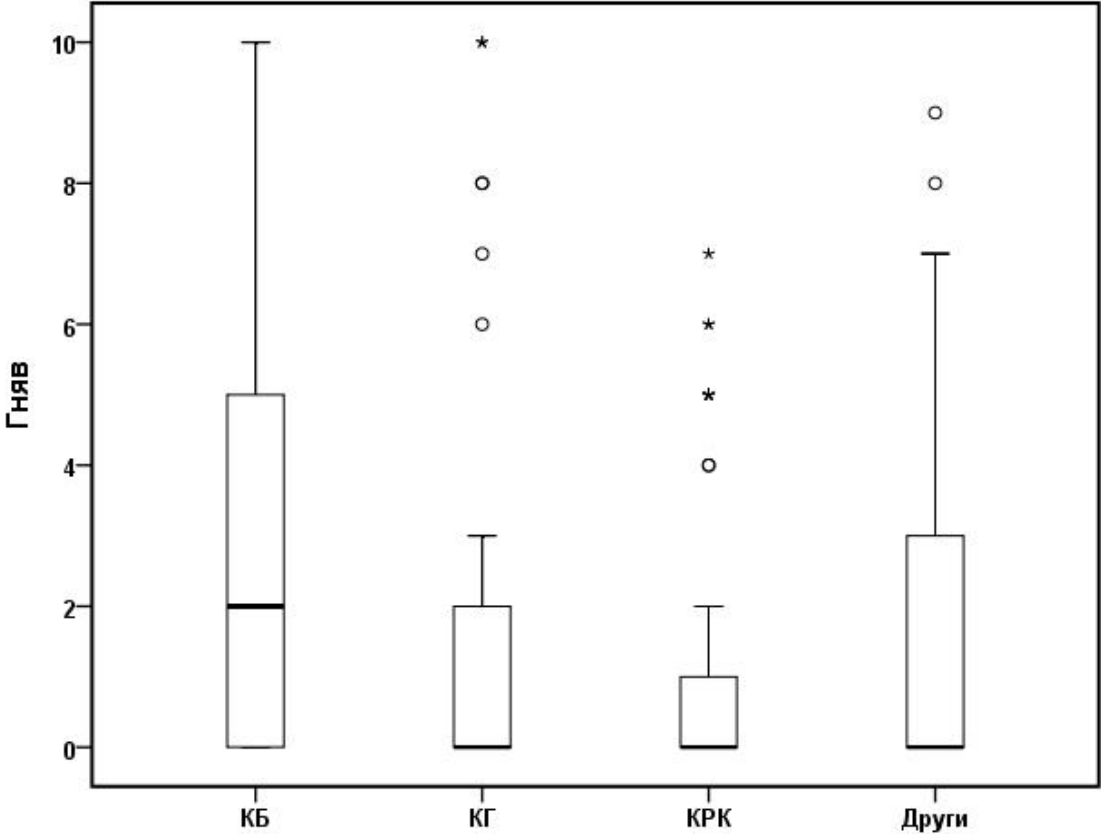
The Mann-Whitney analysis shows that there is a significantly higher level of the feeling of anger in patients with performance status 1 compared to those with performance status 0. (P value -0,002). (Figure16)



thermometer 4 (anger) Performance status

Figure(16). A boxplot illustrating distribution by the general condition of all patients according to the ECOG scale. The abscissa shows the performance status (PS), and the ordinate – the patients’ level of anger.

The Mann-Whitney analysis shows that there is a significantly higher level of anger in patients with lung carcinoma than in the other studied localisations. (Figure17)



Anger

LC BC CRC Other

Figure(17). A boxplot illustrating the level of anger according to tumour localisation. The abscissa shows the studied localisations, and the ordinate – the patients’ level of the feeling of anger.

A single-factor regression analysis shows that the factors sex and performance status can be associated with higher levels of anger, measured with an anger thermometer. (Table 17)

	OR	CI 95%	p-value
Sex	2.13	1.09-4.1	0.026
Family status	3.9	0.66-23.2	0.26
Remoteness	0.61	0.31-1.19	0.15
Age	0.57	0.29-1.11	0.1
Stage	0.77	0.39-1.51	0.4
Performance status	2.33	1.36-5.69	0.003
Lung cancer	2.05	0.83-5.04	0.11
Breast cancer	0.45	0.15-1.35	0.15

Table(17). A single-factor regression analysis of the possibility for the given factors to predict by the high levels of anger among the patient population

The following factors are associated with a higher risk of anger:

Sex (CI 95% 1.09 - 4,1 p= 0,026)

Performance status (CI 95% 1.36 -5.69 p=0,003)

Analysis of the results of the measured levels of the need for help.

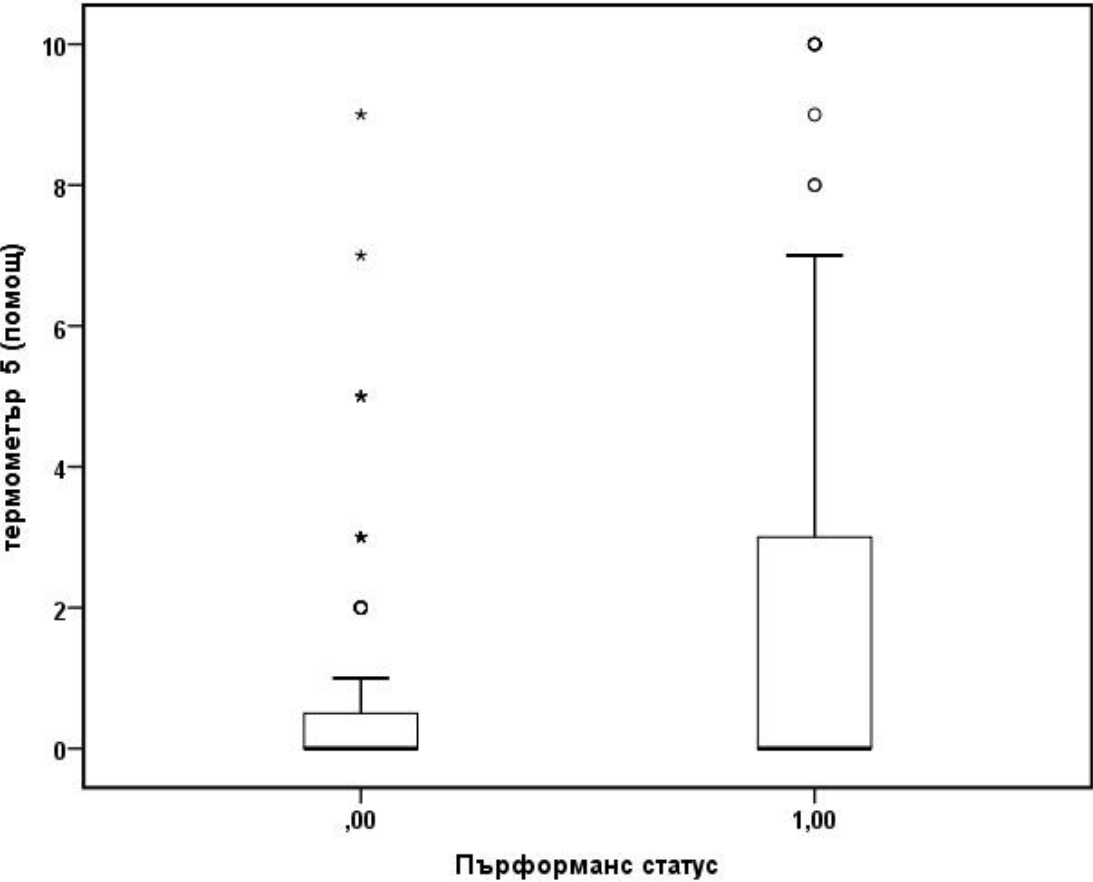
Thirty-two (14.2 %) patients reported a strong need for help.

The chi square analysis of the sociodemographic data shows that there is no dependency between the characteristics age, sex, religion, ethnicity and residence (remoteness from the regional oncological centre) and the level of the need for help, as measured with need-for-help thermometers. A correlation between the performance status, carcinoma localisation and the level of the need for help is observed. (Table 18)

Need-for-help thermometer			
	Low levels of a need for help	High levels of a need for help	P value
Age			0.3
≤65	115	22	
>65	78	10	
Sex			0.9
Men	85	14	
Women	108	18	
Stage			0.03
II and III	94	9	
IV	99	23	
Performance status			0.001
0	96	8	
1	97	24	
Localisation			0.8
Lung	43	10	
Breast cancer	53	8	
Colorectal carcinoma	52	8	
Other (over 14 different localisations)	46	7	

Table (18). Sociodemographic data and their correlation with the need for help

The conducted Mann-Whitney test shows a strong tendency towards a greater need for help in the patients in PS 1 (1.8 ± 2.8) than the patients in PS 0 (0.73 ± 1.6) ($p=0.006$). (Figure18)

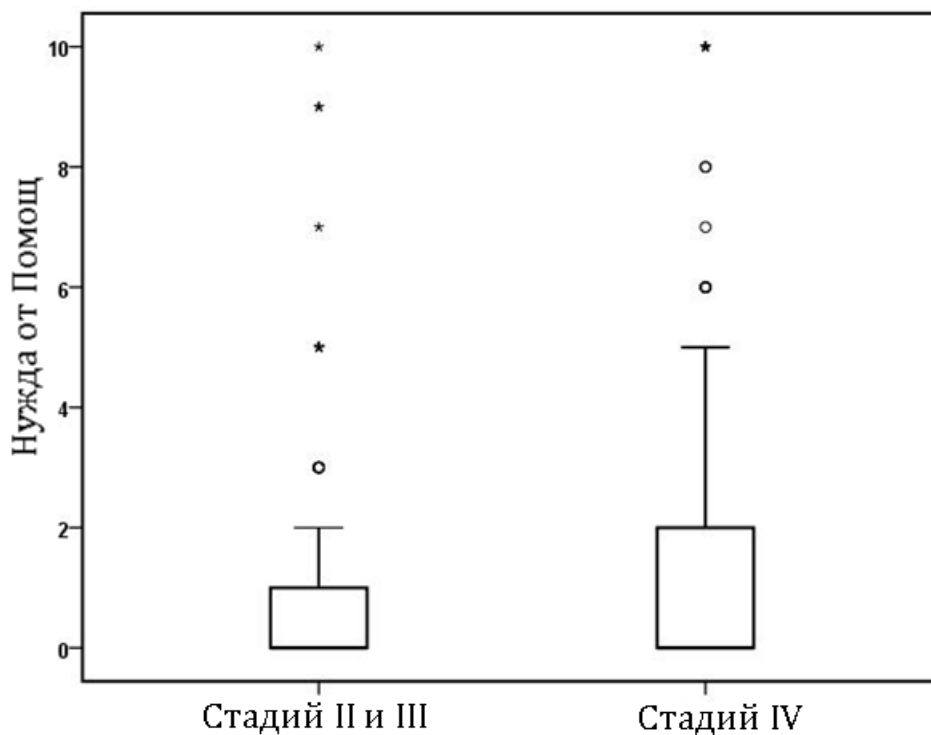


thermometer 5 (help)

Performance status

Figure (18). A boxplot illustrating distribution by the general condition of all patients according to the ECOG scale. The abscissa shows the Performance status (PS), and the ordinate – the level of the patients’ need for help.

The Mann-Whitney analysis shows that there is a significantly higher level of a need for help in patients in the metastatic stage (1.58 ± 2.6) compared to those in an earlier stage (0.97 ± 2.05) ($p=0.08$). (Figure19)



Need for help

Stage II and III

Stage IV

Figure (19). A boxplot illustrating the distribution by the carcinoma stages of all patients. The abscissa shows the stage, and the ordinate – the level of the patients' need for help.

The single-factor regression analysis shows that the factors stage of the disease and performance status may be associated with higher levels of a need for help, as measured with a need-for-help thermometer. (Table 19)

	OR	CI 95%	p-value
Sex	0.98	0.46-2.1	0.9
Family status	1.28	0.22-7.3	0.7
Remoteness	0.45	0.21-0.97	0.042
Age	1.49	0.67-3.2	0.3
Stage	1.70	1.17-2.93	0.034
Performance status	2.23	1.39-6.59	0.002
Lung cancer	1.25	0.43-3.6	0.6
Breast cancer	0.82	0.26-2.54	0.7

Table (19). A single-factor regression analysis of the possibility for the given factors to predict by the high levels of the need for help among the patient population.

The following factors are associated with a higher risk of a need for help:

Performance status (CI 95% 1.39-6.59 p=0.002)

Stage (CI 95% 1.17-2.93 P=0.034)

Correlation and internal consistency among the emotion thermometers

The correlation analysis under Spearman indicates the following dependencies:

*The Distress thermometer is in strong correlation with the Anxiety thermometer, Rho-0.735, and in a moderate correlation with the Depression thermometer, Rho-0,509.

*The Anxiety thermometer is in a strong correlation with the Distress thermometer, Rho-0,735, and in a moderate correlation with the Depression thermometer and the Anger thermometer, Rho-0.544 and Rho-0.403.

*The Depression thermometer indicates a moderate correlation with the Distress, Anxiety and Anger thermometers, with Rho coefficients respectively 0.509...0.544....0.508.

*The Anger thermometer indicates a weak correlation with the Distress and Need-for-Help thermometers, respectively Rho-0.337 and Rho-0.354, and a moderate correlation with the Anxiety and Depression thermometers, respectively Rho- 0.403 and Rho- 508.

*The Need-for-Help thermometer indicates a weak correlation with all other thermometers- respectively thermometers Distress – Rho-0.326, Anxiety – Rho-0.369, Depression – Rho-0.379, and Anger – Rho-0.354. (Table 20)

	Thermometer (anxiety)	Thermometer (depression)	Thermometer (anger)	Thermometer (help)
Spearman's rho	0.735	0.509	0.337	0.326
Distress thermometer	p<0.001	p<0.01	p<0.01	p<0.0

Table (20)

Internal consistency of the thermometers

Cronbach's alpha (α), as an objective rater of the reliability of the employed thermometers, is 0.82, which indicates good internal consistency.

Discussion

Each patient diagnosed with an oncological disease, irrespective of its stage and type, who undergoes treatment or has symptoms, experiences a certain level of distress. According to literature data, a clinically measurable level of distress is observed in about 20-40% of the newly diagnosed patients and of those with proven recurrence. For all oncological diseases, the average level of distress is approximately 35%, which varies by localisations from about 30% in patients with gynaecological malignant diseases to 43% in cases of lung carcinoma. The meta-analyses show that 30-40% of the patients with a different type of tumours manifest some type or a combination of mood disorders. At this stage, there is a problem with the identification of the patients with distress, as well as with the provision of adequate psychosocial help, due to poor preparation of the teams that serve the oncological patients, the lack of information, as well as the fear of the contact with specialists who deal with psychological or psychiatric problems.

There is evidence that the distress, depression and mental disorders vary depending on a number of factors: localisation, stage, sex, ethnicity and age of the patient. Those with a higher risk of development of distress have a medical history of a mental disorder, depression or addictions; they have cognitive impairments, severe comorbidity, poorly controlled symptoms, conditions that hamper/disrupt the communication, problems in the social field. The risk factors of great weight include: young age, female individuals, loners, parents with young children and subjects of abuse. Last but not least, distress also affects the members of the oncological patient's family (or the patient's carer). The screening and efficient early treatment have the potential to reduce the psychosocial distress not only for the patients, but also for their relatives, who love them and take care of them. Due to the fact that distress has a negative effect on the treatment, the quality of life and on the survival, its early screening and timely management improve the

medical treatment. A group of Swiss scientists from the university of Lucerne published a meta-analysis of the use of an “emotion thermometer” for newly diagnosed cancer patients. They concluded that the publications on the study of distress and other emotion thermometers, such as anxiety, anger and a need for help, are rare, especially for young oncological patients. The study conducted by the authors recommends the use of “the emotion thermometers” as a validated screening instrument in newly diagnosed cancer patients.

It is widely known that making a diagnosis and the very treatment of the oncological disease have more than just a physical impact. Various individual reactions to distress have been described, as well as the ability to adapt to it (the ability to manage the subsequent effects). The first manifestation of psychosocial distress in many people may occur as early as the moment in which there is suspicion that the possible diagnosis is cancer and varies in the course of the disease.

Studies covering a wide range of various localisations, different stages and groups of the population have identified the frequency (epidemiology), the distribution and the nature of the distress manifested by oncological patients. Both among the very patients and in the group of the “survivors”, the level of distress has a considerable impact on the quality of life and depends on a number of social, emotional, economic and other factors. Significant levels of distress have been reported in different groups of patients with oncological diseases with frequency varying between 35-45% and reaching up to 70% in patients in palliative care.

The high levels of distress are connected with increased suffering, lower quality of life, difficulty making decisions about the treatment, non-adherence to the treatment, dissatisfaction with the medical care, additional visitations in hospitalisations. The patients do not voluntarily report the manifestations of distress or any type of mental discomfort as they feel embarrassment, fear that they will be stigmatised. Moreover, providers of oncological care often fail to identify the psychosocial problems. On frequent occasions, the psychosocial distress is recognised when the negative stress reaches levels that are critical for the patient. There are a number of problems related to the provision of psychosocial care in oncology, and some of the key factors are the physician’s insufficient knowledge and skills with regard to the psychosocial evaluation and the communication with regard to psychosocial problems.

Recently, an increase has been observed in the number of researches studying the advantages of therapy in case of occurrence of distress and the management of the symptoms ensuing from

it in the course of development of the oncological disease. There is evidence that the interventions have been successful in reducing the level of distress, anxiety, depression, pain and tiredness.[89] it has been established that the psychosocial services for oncological patients lead to a reduction in the costs of up to 22% for the respective healthcare system.

Distress is conceptualised as extending along a continuum – ranging from common, normal feelings of vulnerability, sadness and fears – to problems that can become disabling, such as clinical depression, panic and spiritual crises. In the context of oncology, distress is multi-factorial, as a number of aspects of the patient’s personal life can contribute to feeling distress, including physical symptoms, severity of the disease, ability to perform everyday activities, access to information and support, as well as other personal factors.

At this stage ,it is recommended that the identification of and battling distress be a standard in the overall care for the oncological patients, as there is always a risk of its development in the course of the disease. The concept of battling and managing psychosocial distress, in which the screening for distress is part of the routine everyday practice, is a key aspect which should be introduced on a national level.

The meta-analyses show that 30-40% of the patients with various types of tumours manifest some kind or combinations of mood disorders. Are we sufficiently precise with regard to the patient’s mental status? A number of significant studies from the past two decades have presented data confirming the connection between oncological diseases and the psychological factors, and have established three basic regularities. The first one is that the beginning of the disease coincides in time with significant traumatising events in the individual’s life; the second one is that the treatment of the oncological disease is stressogenic; and the third one – that the personality models for management during the treatment impact not only the patient’s quality of life, but also the prognosis. Thus, in the mid-1070s the official foundations of psycho-oncology were laid. The existence of emotional problems in oncological patients has been described by many authors and in various aspects. It is a widely known fact that making the diagnosis and the very treatment have more than just a physical effect. Various reactions to distress have been described, as well as the ability to adapt to it.

It is precisely the different types of emotional reactions and their correlation with the levels of distress in oncological patients that comprise the subject matter of this dissertation paper. In addition to distress as the main parameter of the emotional reaction, we studied the following

psychoemotional disorders and their correlation with distress, as well as between them – depression, anxiety, anger, and need for help.

The analysis of the results of the measured level of distress shows that the individuals with low level of distress are 114 (50.7%), and those who manifested moderate/high level of distress – 111 (49.3%).

The analysis of the sociodemographic data shows that there is no dependency between the characteristics age, sex, religion, ethnicity and residence (remoteness from the regional oncological centre) and the level of distress measured with the Distress thermometer. A correlation between the performance status – P value 0.006, carcinoma localisation – P-value 0.001, level of education – P value 0.017, and the level of distress is observed.

The analysis of anxiety and its correlation with the sociodemographic data shows that there is no dependency between the characteristics age, sex, religion, ethnicity and residence (remoteness from the regional oncological centre) and the level of anxiety measured with the distress thermometer. A correlation between the performance status – P-value 0.043, type of carcinoma – P-value 0.009, and the level of anxiety is observed.

The analysis of depression and its correlation with the sociodemographic data shows that there is no dependency between the characteristics age, sex, religion, ethnicity and residence (remoteness from the regional oncological centre) and the level of depression measured with the Distress thermometer. A correlation between the performance status – P-value 0.004, carcinoma localisation – P-value 0.005, and the level of depression is observed.

The anger analysis of the sociodemographic data shows that there is no dependency between the characteristics age, sex, religion, ethnicity and residence (remoteness from the regional oncological centre) and the level of anger measured with the Distress thermometer. A correlation between the performance status – P-value 0.002, carcinoma localisation – P-value 0.017, and the level of anger is observed.

The need-for-help analysis of the sociodemographic data shows that there is no dependency between the characteristics age, sex, religion, ethnicity and residence (remoteness from the regional oncological centre) and the level of anger measured with the Distress thermometer. A correlation between the performance status – P-value 0.001, carcinoma stage – P-value 0.03, and the level of need for help is observed.

The correlation dependencies between the different thermometers proved just as interesting: the Distress thermometer is in a strong correlation with the Anxiety thermometer – $Rho=0,735$, and in a moderate correlation with the Depression thermometer – $Rho=0.509$. The Anxiety thermometer is in a strong correlation with the Distress thermometer – $Rho=0.735$, and in a moderate correlation with the Depression thermometer and the Anger thermometer – $Rho=0.544$ and $Rho=0.403$. The Depression thermometer showed a moderate correlation with the Distress, Anxiety and Anger thermometers, with Rho coefficients respectively $0.509...0.544...0.508$. The Anger thermometer indicated a weak correlation with the Distress and Need-for-Help thermometers, respectively $Rho=0.337$ and $Rho=0.354$, and a moderate correlation with the Anxiety and Depression thermometers, respectively $Rho=0.403$ and $Rho=0.508$. The Need-for-Help thermometer showed a weak correlation with all other thermometers - respectively the thermometers for Distress – $Rho=0.326$, Anxiety – $Rho=0.369$, Depression – $Rho=0.379$, and Anger – $Rho=0.354$.

The aforementioned goes to show the complex correlation between the distress provoked by the diagnosis and the forthcoming treatment of the oncological patient and a number of other psychoemotional states which the patient goes through during the entire period of treatment. For the first time in Bulgaria, we compared correlation dependency between distress and the listed emotional states in oncological patients, especially as in the world oncological literature similar studies are still scarce.

Conclusions:

1. 49.3% of the patients have a moderate and high level of distress, which will potentially disrupt the conducted treatment and will worsen the prognosis for such patients
2. The patients in a metastatic and non-metastatic stage of the disease have equal levels of distress. This creates an opportunity for the treating physician to inform the patients well of the stage of the disease and of the possibilities for recovery for the purpose of reducing the levels of distress and improving the patients' quality of life.

3. The following factors are associated with a greater risk of high levels of distress- respectively:

- single (OR 5.3, 95% CI, 1.2-21.3; p=0.02)
- poor performance status (OR 3.09,95%CI,1.5-6.1 ; p=0.001)
- lung carcinoma (OR 4.9, 95% CI, 2.1-11.3;p=0.001)
- breast carcinoma (OR 2.7 , 95% CI, 1.2-6.1; p=0.01)

4. The following factors are associated with a greater risk of high levels of anxiety, respectively:

- divorced (OR 3.43, 95% CI,1.05-11.2;p=0.041)
- poor performance status (OR 1.75, 95% CI,1.016-3.04;p=0.044)
- lung carcinoma (OR 2.94, 95% CI,1.31-6.61;p=0.009)
- breast carcinoma (OR 2.48, 95% CI,1.14-5.39,p=0.02)

5.The following factors are associated with a greater risk of high levels of depression, respectively:

- remoteness from the medical centre (OR 1,44 ,95% CI ,1.03-2.85 p=0.014)
- poor performance status (OR 2.37, 95% CI1.19-4.74 p=0.005)
- lung carcinoma (OR 4.81,95% CI, 1.74-13.2 p=0.002)

6. The following factors are associated with a greater risk of high levels of anger, respectively:

- poor performance status (OR 2.33, 95% CI,0.16-0.69,p=0.003)
- men (OR 2.13,95% CI,1.09-4.1, p=0.026)

7. The following factors are associated with a higher risk of need for help:

Performance status (CI 95% 1.39-6.59 p=0.002)

Stage (CI 95% 1,17-2.93 P=0.034)

Contributions:

1. For the first time in Bulgaria, an analysis of the levels of distress, anxiety, depression, anger and need for help of oncological patients has been conducted by a medical oncologist in collaboration with clinical psychologists.
2. For the first time in Bulgaria, a correlation analysis has been conducted between the levels of distress and the anxiety, depression, anger and the need for help in oncological patients prior to the beginning of their treatment.
3. For the first time in Bulgaria, the factors za high levels of anxiety, depression, anger and need for help have been identified.
4. For the first time in Bulgaria, the reliability of the emotion thermometers to characterise the patients' mental state prior to the beginning of their systematic treatment has been demonstrated.
5. For the first time in Bulgaria, the need for introduction of multidisciplinary teams to the oncological practice for screening the mental status of the oncological patient prior to the initial treatment has been demonstrated.

REFERENCES

1. Ferlay, J., et al., *Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012*. Int J Cancer, 2015. **136**(5): p. E359-86.
2. Siegel, R., et al., *Cancer statistics, 2014*. CA Cancer J Clin, 2014. **64**(1): p. 9-29.
3. Ferlay, J., et al., *Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012*. Eur J Cancer, 2013. **49**(6): p. 1374-403.
4. Hendriks, J.M. and P.E. Van Schil, *Isolated lung perfusion for the treatment of pulmonary metastases*. Surg Oncol, 1998. **7**(1-2): p. 59-63.
5. Wong, M., S.P. Choo, and E.H. Tan, *Travel warning with capecitabine*. Ann Oncol, 2009. **20**(7): p. 1281.
6. Keating, G.M. and A. Santoro, *Sorafenib: a review of its use in advanced hepatocellular carcinoma*. Drugs, 2009. **69**(2): p. 223-40.
7. Kobayashi, K. and K. Hagiwara, *Epidermal growth factor receptor (EGFR) mutation and personalized therapy in advanced nonsmall cell lung cancer (NSCLC)*. Target Oncol, 2013. **8**(1): p. 27-33.
8. Rini, B.I., *Vascular endothelial growth factor-targeted therapy in renal cell carcinoma: current status and future directions*. Clin Cancer Res, 2007. **13**(4): p. 1098-106.
9. Fallowfield, L., et al., *Psychiatric morbidity and its recognition by doctors in patients with cancer*. Br J Cancer, 2001. **84**(8): p. 1011-5.
10. Holland, J.C., *American Cancer Society Award lecture. Psychological care of patients: psycho-oncology's contribution*. J Clin Oncol, 2003. **21**(23 Suppl): p. 253s-265s.
11. Jacobsen, P.B. and H.S. Jim, *Psychosocial interventions for anxiety and depression in adult cancer patients: achievements and challenges*. CA Cancer J Clin, 2008. **58**(4): p. 214-30.
12. Hawkins, N.A., et al., *Use of Medications for Treating Anxiety and Depression in Cancer Survivors in the United States*. J Clin Oncol, 2017. **35**(1): p. 78-85.
13. Funk, R., et al., *What happens after distress screening? Patterns of supportive care service utilization among oncology patients identified through a systematic screening protocol*. Support Care Cancer, 2016. **24**(7): p. 2861-8.
14. Mehnert, A., et al., *One in two cancer patients is significantly distressed: Prevalence and indicators of distress*. Psychooncology, 2018. **27**(1): p. 75-82.
15. Traeger, L., et al., *Race by sex differences in depression symptoms and psychosocial service use among non-Hispanic black and white patients with lung cancer*. J Clin Oncol, 2014. **32**(2): p. 107-13.
16. Krebber, A.M., et al., *Screening for psychological distress in follow-up care to identify head and neck cancer patients with untreated distress*. Support Care Cancer, 2016. **24**(6): p. 2541-8.
17. Mitchell, A.J., et al., *Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies*. Lancet Oncol, 2011. **12**(2): p. 160-74.
18. Zabora, J., et al., *The prevalence of psychological distress by cancer site*. Psychooncology, 2001. **10**(1): p. 19-28.
19. Ringwald, J., et al., *Psychological Distress, Anxiety, and Depression of Cancer-Affected BRCA1/2 Mutation Carriers: a Systematic Review*. J Genet Couns, 2016. **25**(5): p. 880-91.

20. Hirschberg, A.M., G. Chan-Smutko, and W.F. Pirl, *Psychiatric implications of cancer genetic testing*. *Cancer*, 2015. **121**(3): p. 341-60.
21. in *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs*, N.E. Adler and A.E.K. Page, Editors. 2008: Washington (DC).
22. Pirl, W.F., et al., *Depression and survival in metastatic non-small-cell lung cancer: effects of early palliative care*. *J Clin Oncol*, 2012. **30**(12): p. 1310-5.
23. Russ, T.C., et al., *Association Between Psychological Distress and Liver Disease Mortality: A Meta-analysis of Individual Study Participants*. *Gastroenterology*, 2015. **148**(5): p. 958-966 e4.
24. Carlson, L.E. and B.D. Bultz, *Cancer distress screening. Needs, models, and methods*. *J Psychosom Res*, 2003. **55**(5): p. 403-9.
25. Soborg, B., et al., *Comparison of screening procedures for Mycobacterium tuberculosis infection among patients with inflammatory diseases*. *J Rheumatol*, 2009. **36**(9): p. 1876-84.
26. Spiegel, D., *Mind matters in cancer survival*. *Psychooncology*, 2012. **21**(6): p. 588-93.
27. Sharpe, M., et al., *Major depression in outpatients attending a regional cancer centre: screening and unmet treatment needs*. *Br J Cancer*, 2004. **90**(2): p. 314-20.
28. Handzo, G., *Spiritual care for palliative patients*. *Curr Probl Cancer*, 2011. **35**(6): p. 365-71.
29. Grassi, L., et al., *Educational intervention in cancer outpatient clinics on routine screening for emotional distress: an observational study*. *Psychooncology*, 2011. **20**(6): p. 669-74.
30. Mitchell, A.J., *Pooled results from 38 analyses of the accuracy of distress thermometer and other ultra-short methods of detecting cancer-related mood disorders*. *J Clin Oncol*, 2007. **25**(29): p. 4670-81.
31. Zabora, J., et al., *A new psychosocial screening instrument for use with cancer patients*. *Psychosomatics*, 2001. **42**(3): p. 241-6.
32. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale*. *Acta Psychiatr Scand*, 1983. **67**(6): p. 361-70.
33. Watson, L., et al., *Evaluating the Impact of Provincial Implementation of Screening for Distress on Quality of Life, Symptom Reports, and Psychosocial Well-Being in Patients With Cancer*. *J Natl Compr Canc Netw*, 2016. **14**(2): p. 164-72.
34. Wells-Di Gregorio, S., et al., *The James Supportive Care Screening: integrating science and practice to meet the NCCN guidelines for distress management at a Comprehensive Cancer Center*. *Psychooncology*, 2013. **22**(9): p. 2001-8.
35. Berry, D.L., et al., *The electronic self report assessment and intervention for cancer: promoting patient verbal reporting of symptom and quality of life issues in a randomized controlled trial*. *BMC Cancer*, 2014. **14**: p. 513.
36. Carlson, L.E., et al., *Online screening for distress, the 6th vital sign, in newly diagnosed oncology outpatients: randomised controlled trial of computerised vs personalised triage*. *Br J Cancer*, 2012. **107**(4): p. 617-25.
37. Lundy, J.J., S.J. Coons, and N.K. Aaronson, *Testing the measurement equivalence of paper and interactive voice response system versions of the EORTC QLQ-C30*. *Qual Life Res*, 2014. **23**(1): p. 229-37.
38. Miller, M.F., et al., *Demonstrating the psychometric properties of a problem-related distress screener in a community sample of 319 cancer survivors*. *Psychooncology*, 2013. **22**(6): p. 1249-57.
39. Meijer, A., et al., *Effects of screening for psychological distress on patient outcomes in cancer: a systematic review*. *J Psychosom Res*, 2013. **75**(1): p. 1-17.

40. Bultz, B.D. and L.E. Carlson, *A commentary on 'effects of screening for psychological distress on patient outcomes in cancer: a systematic review'*. J Psychosom Res, 2013. **75**(1): p. 18-9.
41. Hollingworth, W., et al., *Are needs assessments cost effective in reducing distress among patients with cancer? A randomized controlled trial using the Distress Thermometer and Problem List*. J Clin Oncol, 2013. **31**(29): p. 3631-8.
42. Braeken, A.P., et al., *Psychosocial screening effects on health-related outcomes in patients receiving radiotherapy. A cluster randomised controlled trial*. Psychooncology, 2013. **22**(12): p. 2736-46.
43. Ma, X., et al., *The diagnostic role of a short screening tool--the distress thermometer: a meta-analysis*. Support Care Cancer, 2014. **22**(7): p. 1741-55.
44. Thalen-Lindstrom, A., et al., *Validation of the Distress Thermometer in a Swedish population of oncology patients; accuracy of changes during six months*. Eur J Oncol Nurs, 2013. **17**(5): p. 625-31.
45. Wang, Y., et al., *Measurement of distress in Chinese inpatients with lymphoma*. Psychooncology, 2013. **22**(7): p. 1581-6.
46. Zwahlen, D., et al., *Screening cancer patients' families with the distress thermometer (DT): a validation study*. Psychooncology, 2008. **17**(10): p. 959-66.
47. Wagner, L.I., et al., *Screening for depression in cancer patients receiving radiotherapy: Feasibility and identification of effective tools in the NRG Oncology RTOG 0841 trial*. Cancer, 2017. **123**(3): p. 485-493.
48. de Ruiter, M.B. and S.B. Schagen, *Functional MRI studies in non-CNS cancers*. Brain Imaging Behav, 2013. **7**(4): p. 388-408.
49. Wefel, J.S., et al., *Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults*. CA Cancer J Clin, 2015. **65**(2): p. 123-38.
50. Amidi, A., et al., *Long-term subjective cognitive functioning following adjuvant systemic treatment: 7-9 years follow-up of a nationwide cohort of women treated for primary breast cancer*. Br J Cancer, 2015. **113**(5): p. 794-801.
51. Trask, P.C., *Assessment of depression in cancer patients*. J Natl Cancer Inst Monogr, 2004(32): p. 80-92.
52. Deprez, S., et al., *Longitudinal assessment of chemotherapy-induced alterations in brain activation during multitasking and its relation with cognitive complaints*. J Clin Oncol, 2014. **32**(19): p. 2031-8.
53. Ahles, T.A., *Cognitive changes associated with cancer and cancer treatment*. Semin Oncol Nurs, 2013. **29**(4): p. 229-31.
54. Lotfi-Jam, K., et al., *Profile and predictors of global distress: can the DT guide nursing practice in prostate cancer? Palliat Support Care, 2014. 12(1): p. 5-14.*
55. Wefel, J.S., et al., *The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial*. Cancer, 2004. **100**(11): p. 2292-9.
56. Wefel, J.S., et al., *'Chemobrain' in breast carcinoma?: a prologue*. Cancer, 2004. **101**(3): p. 466-75.
57. Jean-Pierre, P., et al., *Prevalence of self-reported memory problems in adult cancer survivors: a national cross-sectional study*. J Oncol Pract, 2012. **8**(1): p. 30-4.
58. Gehring, K., J.A. Roukema, and M.M. Sitskoorn, *Review of recent studies on interventions for cognitive deficits in patients with cancer*. Expert Rev Anticancer Ther, 2012. **12**(2): p. 255-69.

59. Hermelink, K., et al., *Elucidating pretreatment cognitive impairment in breast cancer patients: the impact of cancer-related post-traumatic stress*. J Natl Cancer Inst, 2015. **107**(7).
60. Conklin, H.M., et al., *Acute neurocognitive response to methylphenidate among survivors of childhood cancer: a randomized, double-blind, cross-over trial*. J Pediatr Psychol, 2007. **32**(9): p. 1127-39.
61. Davis, J., et al., *Emerging pharmacotherapy for cancer patients with cognitive dysfunction*. BMC Neurol, 2013. **13**: p. 153.
62. Gehring, K., et al., *A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor*. J Neurooncol, 2012. **107**(1): p. 165-74.
63. Kohli, S., et al., *The effect of modafinil on cognitive function in breast cancer survivors*. Cancer, 2009. **115**(12): p. 2605-16.
64. Lundorff, L.E., B.H. Jonsson, and P. Sjogren, *Modafinil for attentional and psychomotor dysfunction in advanced cancer: a double-blind, randomised, cross-over trial*. Palliat Med, 2009. **23**(8): p. 731-8.
65. Fitchett, G., P.M. Meyer, and L.A. Burton, *Spiritual care in the hospital: who requests it? Who needs it?* J Pastoral Care, 2000. **54**(2): p. 173-86.
66. Vardy, J., et al., *Cancer and cancer-therapy related cognitive dysfunction: an international perspective from the Venice cognitive workshop*. Ann Oncol, 2008. **19**(4): p. 623-9.
67. Linden, W., et al., *Anxiety and depression after cancer diagnosis: prevalence rates by cancer type, gender, and age*. J Affect Disord, 2012. **141**(2-3): p. 343-51.
68. Rodin, G., et al., *Traumatic stress in patients with acute leukemia: A prospective cohort study*. Psychooncology, 2018. **27**(2): p. 515-523.
69. Faller, H., et al., *Effects of psycho-oncologic interventions on emotional distress and quality of life in adult patients with cancer: systematic review and meta-analysis*. J Clin Oncol, 2013. **31**(6): p. 782-93.
70. Regier, D.A., *Mental disorder diagnostic theory and practical reality: an evolutionary perspective*. Health Aff (Millwood), 2003. **22**(5): p. 21-7.
71. Howell, D., et al., *A pan-Canadian practice guideline and algorithm: screening, assessment, and supportive care of adults with cancer-related fatigue*. Curr Oncol, 2013. **20**(3): p. e233-46.
72. Lustberg, M.B., R.E. Reinbolt, and C.L. Shapiro, *Bone health in adult cancer survivorship*. J Clin Oncol, 2012. **30**(30): p. 3665-74.
73. Andersen, B.L., et al., *Psychologic intervention improves survival for breast cancer patients: a randomized clinical trial*. Cancer, 2008. **113**(12): p. 3450-8.
74. Wood, M.E., et al., *Second malignant neoplasms: assessment and strategies for risk reduction*. J Clin Oncol, 2012. **30**(30): p. 3734-45.
75. Neu, P., et al., *Time-related cognitive deficiency in four different types of depression*. Psychiatry Res, 2001. **103**(2-3): p. 237-47.
76. de Kwaasteniet, B., et al., *Relation between structural and functional connectivity in major depressive disorder*. Biol Psychiatry, 2013. **74**(1): p. 40-7.
77. Campbell, S., et al., *Lower hippocampal volume in patients suffering from depression: a meta-analysis*. Am J Psychiatry, 2004. **161**(4): p. 598-607.
78. Li, M., P. Fitzgerald, and G. Rodin, *Evidence-based treatment of depression in patients with cancer*. J Clin Oncol, 2012. **30**(11): p. 1187-96.
79. Stark, D., et al., *Anxiety disorders in cancer patients: their nature, associations, and relation to quality of life*. J Clin Oncol, 2002. **20**(14): p. 3137-48.

80. Peck, A., *Emotional reactions to having cancer*. CA Cancer J Clin, 1972. **22**(5): p. 284-91.
81. Holland, J.C., *Psycho-oncology: Overview, obstacles and opportunities*. Psychooncology, 2018. **27**(5): p. 1364-1376.
82. Kissane, D., *Beyond the psychotherapy and survival debate: the challenge of social disparity, depression and treatment adherence in psychosocial cancer care*. Psychooncology, 2009. **18**(1): p. 1-5.
83. Herschbach, P., et al., *Psychological problems of cancer patients: a cancer distress screening with a cancer-specific questionnaire*. Br J Cancer, 2004. **91**(3): p. 504-11.
84. Iwamitsu, Y., et al., *Anxiety, emotional suppression, and psychological distress before and after breast cancer diagnosis*. Psychosomatics, 2005. **46**(1): p. 19-24.
85. Steinberg, T., et al., *Prevalence of emotional distress in newly diagnosed lung cancer patients*. Support Care Cancer, 2009. **17**(12): p. 1493-7.
86. Iconomou, G., et al., *Prospective assessment of emotional distress, cognitive function, and quality of life in patients with cancer treated with chemotherapy*. Cancer, 2004. **101**(2): p. 404-11.
87. Escartin, A., et al., *Acute Cholecystitis in Very Elderly Patients: Disease Management, Outcomes, and Risk Factors for Complications*. Surg Res Pract, 2019. **2019**: p. 9709242.
88. Hoffman, K.E., et al., *Psychological distress in long-term survivors of adult-onset cancer: results from a national survey*. Arch Intern Med, 2009. **169**(14): p. 1274-81.
89. Cunningham, A.J., *Adjuvant psychological therapy for cancer patients: putting it on the same footing as adjunctive medical therapies*. Psychooncology, 2000. **9**(5): p. 367-71.
90. Barroso, J., J.R. Carlson, and J. Meynell, *Physiological and psychological markers associated with HIV-related fatigue*. Clin Nurs Res, 2003. **12**(1): p. 49-68.
91. Ernstmann, N., et al., *Determinants and implications of cancer patients' psychosocial needs*. Support Care Cancer, 2009. **17**(11): p. 1417-23.
92. Kahn, K.L., et al., *Patient centered experiences in breast cancer: predicting long-term adherence to tamoxifen use*. Med Care, 2007. **45**(5): p. 431-9.
93. Mitchell, A.J., et al., *Prevalence and predictors of post-stroke mood disorders: A meta-analysis and meta-regression of depression, anxiety and adjustment disorder*. Gen Hosp Psychiatry, 2017. **47**: p. 48-60.