PSYCHOLOGICAL DISORDERS IN RELATION TO PAIN SYNDROME IN PATIENTS WITH COLORECTAL CANCER

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Abstract:

Aim. The principle aim is to investigate the relationship between psychological distress, pain syndrome and clinical features in colorectal cancer patients.

Methods. The study assessed forty-nine patients undergoing chemotherapy from Cancer Institute "Ion Chiricuta" Cluj-Napoca admitted between 2016 and 2017 with locally advanced or metastatic colorectal cancer. For each patient, pain intensity was evaluated using a visual analogue scale, whereas depression and anxiety levels were evaluated using Beck Depression and State-Trait Anxiety Inventories. All evaluations were determined at their first presentation in the hospital before treatment initiation. Correlations between demographic characteristics, pain evaluation and mental disorders were realized using Chi-squared tests ($\chi 2$) and Spearman's rho.

Results. Pain was observed in 76% of patients, 54% of whom had moderate to increased pain. Twenty-nine percent of patients presented with nociceptive pain, whereas 20% had neuropathic pain. In 27% of patients, the pain was mixed. Depression was moderate to severe in 53% of patients, and high levels of anxiety were found in 24% of patients. Levels of anxiety and depression did not correlate with demographic characteristics. There were correlations between the pain type and its level. Neuropathic pain correlated with moderate pain, while mixed pain was correlated with intense pain (p=0.0003). Tumor site was correlated with level of anxiety: colorectal cancer was associated with mild anxiety, rectal cancer was associated with moderate anxiety, and patients with anal canal cancer presented increased anxiety (p=0.026).

Conclusion. High pain frequency is associated with high anxiety and depression levels in colorectal cancer patients. Pain intensity is correlated with pain type, while psychological disorders are correlated with tumor site.

Key-words: *colorectal cancer; psychological distress; depression; anxiety; pain*

Core tip.

Colorectal cancer is the second most common type of cancer in both women and men. Pain is a frequent symptom observed due to tumor evolution or treatment side effects. Psycho-emotional disorders are common, making the treatment of pain syndrome a challenge. We investigated the relationship between psychological distress, pain syndrome and clinical features in colorectal cancer patients using questionnaires never used with this type of patient. Our results suggested that pain is a frequent symptom, anxiety and depression levels were increased and correlate with tumor site; hence, these tests may be used in colorectal patients.

Introduction

Colorectal cancer CRC is one of the most prevalent causes of cancer-associated deaths worldwide, with a 5-year rate of survival of approximately 60%. More than half of patients develop metastatic disease, with a life expectancy of approximately 30 months [14]. Approximately 30% of patients undergoing treatment for malignancies experience psychological symptoms of distress [21]. In these patients, the presence of psychological distress can interfere with treatment compliance and quality of life.

Distress can range from sadness and fear to disabling problems, such as depression, anxiety, social isolation and spiritual crisis [29]. Depression in cancer patients is commonly

found due to diagnosis, side effects of treatment or different refractory symptoms that affect quality of life. In patients with advanced or metastatic CRC, anxiety and depression are found as a consequence of either treatment or tumor evolution responsible for pain syndrome, chronic fatigue or bowel disorders [12]. These symptoms are associated with decreased compliance with treatment and a decreased health-related quality of life [22]. Although different studies have revealed the presence of depression in CRC patients, there is no valid method for assessing psychological disorders in cancer patients.

Pain is a subjective experience and is the most common disease symptom. Cancer patients experience different types of pain regarding its intensity and characteristics. The perception of pain depends on many factors, including the mechanism of production, intensity of pain, cultural, social and spiritual aspects [23, 25]. Cancer pain management is complex, as cancer-associated pain consists of a syndrome that includes sensitive-sensorial, cognitive, emotional and behavioral aspects. A few studies have evaluated psychological disorders in colorectal cancer, but none have investigated the relationship between distress and pain syndrome or clinical pathologist features in CRC.

The objective of our study was to evaluate pain syndrome and its correlations with anxiety and depression in patients with advanced or metastatic CRC from The Oncology Institute "Prof. Dr. Ion Chiricuță" Cluj-Napoca, Romania.

Materials and methods

Forty-nine patients with metastatic or advanced CRC from our institution were included in the study. The Ethics Committee of the Cancer Institute "Prof. Dr. Ion Chiricuta" and Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania approved the study, and all patients signed a consent form.

For each patient, the intensity of pain was evaluated using a visual analogue scale (VAS), which consists of a graded horizontal line of 10 cm on which the patient marks the point representative for the perception of their current pain. Projection of pain on the silhouette and multiple-choice questions were used to evaluate the type of pain depending on the mechanism of production and corporeal perception. The intensity of pain was considered mild at VAS scores from 3-4; score from 5-7 indicated moderate pain; and scores from 8-10 indicated severe pain.

Depression and anxiety were assessed through questionnaires at the beginning of treatment. Levels were measured by applying the Beck Depression and State-Trait Anxiety Inventory. Beck Depression Inventory (BDI) is a 21-item self-report rating inventory that measures characteristic attitudes and symptoms of depression [3]. The State-Trait Anxiety Scale evaluates the level of anxiety. It consists of 40 items, 20 items allocated to State Anxiety (S-Anxiety) and the other half to Trait Anxiety (T-Anxiety) subscales. Items from the S-Anxiety scale assess the intensity of current feelings or anxiety caused by an event, whereas items from the T-Anxiety scale assess the level of anxiety as a characteristic. Scores between 20 and 35 represent minimum, 35-50 mild, 50-65 high and 65-80 extremely high anxiety [6].

Correlations between demographic characteristics, pain evaluation and mental disorders were conducted using Chi-squared test ($\chi2$) and Spearman's rho. All statistical analyses were performed by a biomedical statistician.

Results:

Of the 49 patients included in the study, 65% were males, and 35% were females. The patient's age ranged from 24-78 years, with a mean age of 63 years. Regarding living areas, 78% of patients came from urban areas, whereas 23% of patients came from rural areas (Table 1).

Regarding primary tumor location, 63% of patients had colon tumors, 33% had rectal tumors, and 4% had anal canal tumors.

Sixteen percent of patients were diagnosed with advanced CRC (stage III), whereas 84% were diagnosed with metastatic CRC. The localization of metastases was predominantly in the liver (48%), other included lung (7%), peritoneum (10%), bone (2%), and lymph nodes (7%) and multiple metastases (24%) (Table 1).

Number of patients	49
Age years	
Median	63
Range	24-78
Gender	
Male	32
Female	17
Provenience	
Urban	38
Rural	11
Tumor location	
Colon	31
Rectum	16
Anal canal	2
Stage	
Locally advanced (III)	7
Metastatic (IV)	42
Site of metastases	
Liver	20
Lung	3
Peritoneal	4
Bone	1
Ovarian	1
Lymphnode	3
Multiple sites	10

Table 1. Patient's characteristics

without any symptoms at the moment of the questionnaire. Of the patients who experienced pain, 45% had mild pain (VAS 0-4), 43% presented moderate pain (VAS 5-7) and 12% had increased pain (VAS>8).

Depression was mild in 47% of patients, moderate in 45% of patients and severe in 8% of patients. Anxiety was mild in 22% of patients, moderate in 53% of patients and high in 24% of patients (Table 2).

Number of patients	49
Pain intensity	
Mild (VAS 0-4)	22
Moderate (VAS 5-7)	21
Severe (VAS>8)	6
Type of pain	
Neuropathic	10
Nociceptive	14
Mixed	13
Anxiety (STAI)	
Mild (35-50)	11
High (56-65)	26
Extremely high (65-80)	12
Depression (BDI)	
Mild (0-7)	23
Moderate (8-10)	22
Severe (11-21)	4

Table 2. Pain, depression and anxiety score of study patients

Concerning the characteristics of pain, 29% of patients presented nociceptive pain and 20% presented neuropathic pain, while 27% of patients presented mixed pain. Twenty-four percent of patients had good pain management

In our group, there were no correlations between levels of depression, anxiety, intensity of pain and demographic characteristics of patients (Table 3, 4).

	Depression			Chi-squared test χ2	p-value
	Mild	**Moderate**	**Severe**		
Age					
>65	10	7	3	0.254	
<65	13	15	1		
Stage					
3	2	5	1	0.39	
4	21	17	3		
Demographic characteristics					
Rural	4	6	-	0.41	
Urban	17	15	4		
Pain intensity VAS					
Mild	16	17	-	0.052	
Moderate	5	4	3		

Severe	2	1	1	
Anxiety STAI 1				
Mild	8	3		
Medium	13	11	2	0.09
High	2	8	2	
Anxiety STAI 2				
Mild	3	-	-	
Medium	16	13	2	0.179
High	4	9	2	
Pain type				
Without	6	6	-	
Mixt	6	6	1	0.89
Neuropathic	4	5	1	
Nociceptive	7	5	2	

Table 3. Correlations between depression and patient's characteristic

	Anxiety STAI 2				
	Mild	**Moderate**	**Severe**	Chi-squared test χ2	p-value
Age					
>65	1	14	5	0.71	
<65	2	17	10		
Sex					
Feminine	-	9	8	0.11	
Masculine	3	22	7		
Stage				0.005	
3	1	1	6		
4	2	30	9		
Demographic characteristics					
Rural	-	4	6	0.1	
Urban	2	25	9		
Pain intensity VAS					
Mild	2	20	11	0.97	
Moderate	1	8	3		
Severe	-	3	1		
Pain type					
Without	1	7	4		
Mixt	-	9	4	0.96	
Neuropathic	1	6	3		
Nociceptive	1	9	4		

Table 4. Correlations between anxiety and patient's characteristics

There was no statistically significant difference regarding the level of depression or anxiety between the age group. Regarding patient gender, women and men experience the same level of depression and anxiety (p=0.41)

In addition, using Spearman's rho test, correlations between the type of pain and the level of pain were revealed. Neuropathic pain correlated with VAS of 3-5, nociceptive pain correlated with VAS 6-8 and mixed pain correlated with VAS >8, (p=0.0003) (Table 5).

Correlations	Spearman's rho P-value
Pain levels and pain type	0,005
STAI 1 and tumor site	0,026
STAI 2 and tumor site	0,026

Table 5. Spearman's rho test interpretation of variables

Moreover, significant correlations were revealed between tumor site and levels of anxiety. Colon cancer correlated with mild anxiety, rectal cancer with moderate anxiety and anal cancer with increased anxiety (p=0.026). Furthermore, the same correlation was observed when assessing the ongoing T-Anxiety inventory (Table 6).

Reference (Country)	Patients number	%Inadequate treatment	95% CI
Sabatowski (Germany) [24]	905	13	11-15
Uki (Japan) [25]	121	27	20-36
Wells (USA) [26]	139	29	22-37
Cascinu (Italy) [27]	117	43	34-52
Larue (France) [28]	270	51	45-57
Palalogos (Romania) [23]	52	62	56-67
Cleeland (USA) [21]	281	65	59-70
Mystakidou (Greece) [29]	220	75	69-80
Saxena (India) [30]	200	79	73-84

Table 6. Statistical data of other studies of inadequate treatment

Discussion:

Colorectal cancer remains an important health problem worldwide. The quality of life of patients with locally advanced or metastatic CRC depends on many factors, including the presence of symptoms, social, spiritual and cultural aspects. Pain syndromes and psychological disorders are often under-evaluated in these patients, causing the management of treatment very difficult. Current methods used for evaluating depression and anxiety in different diseases are heterogeneous, and in patients with cancer, there are no standard methods for this purpose.

STAI has been used extensively in a number of chronic medical conditions, including rheumatic conditions such as rheumatoid arthritis, systemic lupus erythematosus, fibromyalgia, and musculo-skeletal conditions [26, 28, 30]. Hospital, anxiety, and depression scale (HADS) score is a screening instrument for anxiety and depression and has been validated in different settings for the general population and patients with a wide range of medical conditions [23, 2]. It is a self-administered questionnaire with the ability to detect minor psychiatric impairment. In addition, the Beck Anxiety Inventory (BAI) is a brief measure of anxiety with a focus on somatic symptoms of anxiety that was developed as a measure adept at discriminating between anxiety and depression. BAI includes assessment of symptoms such as nervousness, dizziness, inability to relax, with 21 items. Increasing use of this measure has been observed in a number of rheumatic conditions, including fibromyalgia and arthritis [17, 20].

In our study, we used anxiety and depression assessment STAI and BDI questionnaires. Similar to other studies, we revealed a high incidence of anxiety and depression in patients with CRC; more than 50% of patients experience moderate and high levels of psychological disorders [10, 25].

Our results are similar to those reported by Diego Miranda et al., who described psychological disorders in 55% of patients. Anxiety and depression are considered the most important psychological co-morbidities and are associated with low compliance to treatment, decreased quality of life and finally decreased survival in patients with cancer [15].

Current methods of evaluating depression and anxiety are heterogeneous, and in cancer patients, there are no standard methods for this purpose. Those used in our study have proved

their efficacy in other pathologies where they have been validated. The prevalence of depression in our study was similar to that observed by other authors in CRC patients using different methods.

Pain syndrome often represents the first symptom of a tumor. The mechanism by which pain is produced represents an important factor for clinical presentation and treatment. Depending on the mechanism of production, pain is classified as nociceptive, produced through the activation of nociceptors by inflammatory substances such as serotonin, P substance, bradykinin, prostaglandins, histamine and neuropathic pain, caused by injury of nervous fibers [4].

For the description of neuropathic pain, patients use words such as burning, painfully cold sensation, and electric shock. Nociceptive pain is described as sharp, aching, or throbbing pain according to the McGill questionnaire [11]. The perception of pain depends on several factors, including the mechanism of production, education, cultural and social conditions or painful past, which explain the complexity of pain management.

There are several tools for evaluating pain levels. Some methods are unidimensional, simple, repeatable, such as the Simple Verbal Scale (SVS), Visual Analog Scale (VAS), and Numeric Scale (NS), which evaluate only the pain intensity. Others are complex, multidimensional and associate language, anxiety and depression questionnaires (BDI, HADS), and projecting pain on the silhouette [7]. The Pain Management Index (PMI) is a score linking analgesic treatment to the intensity of pain as a measure of treatment adequacy for cancer pain [1].

Several elements of pain must be evaluated to better understand the syndrome as a whole. These consist of evaluating the pain history, contributing factors, temporary or continuous, frequency of the pain episodes, topography, intensity and type of pain, analgesics that have been used and their efficacy. In addition, the details of psychosocial, emotional and cognitive impacts are significant. Clinical and paraclinical examinations, such as searching for areas with shortages of sensitive or motor functions, paresthesia, allodynia,

hyperalgesia, suggest nervous fiber injury.

Similar to other studies, we found a high incidence of pain in CRC (76%); 56% of CRC patients reported having moderate to increased pain. Regarding the pain characteristics, 27% had mixed pain, neuropathic associated with nociceptive pain. The study is the first to describe the association between the level of pain and type of pain, with increased pain being associated with mixt pain. In addition, the intensity of pain correlates with depression (p=0.05).

Another interesting result of our study is the correlation between the localization of tumors and psychological disorders. Colon cancer has been correlated with mild anxiety, rectal cancer with moderate anxiety and anal cancer was associated with high anxiety (p=0.026).

Data from the literature have shown that over 70% of patients with cancer experience moderate to severe pain during their illness, and only a small proportion of patients receive adequate analgesia. The efficacy of treatment should be evaluated by calculating the Pain Management Index (PMI).

Insufficient treatment of cancer pain syndrome is an important healthcare problem worldwide despite the elaboration of several guidelines for cancer pain management. Many factors contribute to these phenomena depending on health care providers or patients, family and society. In the literature, the efficacy of analgesics in cancer-related pain varies from 13% to 79% (Table 5). In our institution, untreated pain was previously reported in 63% of CRC patients [16].

The under treatment of cancer-related pain is present worldwide depending on many socioeconomic reasons. Patient culture, access to medical services, omission of communicating the pain to the doctor, reluctance for physicians to prescribe and patients to use opioids because of their known side effects are some of the examples [9]. These obstacles should be overcome by emphasizing the importance of pain control in cancer patients. A good evaluation of pain syndrome depending on the etiology of pain must be performed along with the assessment of pain intensity by using

appropriate pain evaluation forms at the beginning of the treatment but also after pain therapy to assure its control. Moreover, patients must be ensured with adequate information about opioid use and other analgesic administration.

Our study revealed correlations between perception and pain intensity, psychological disorders and tumor site. Perception of pain depends on the patient's previous pain history, cultural, religious factors and psychological disorders. It is important to have a holistic evaluation of patients to provide better counseling and correct management of the oncology pathology.

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

Bibliografie:

[1]   Azevedo Sao Leao Ferreira K, Kimura M, Jacobsen Teixeira M. The who analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it? Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 2006; 14: 1086-1093 [PMID: 16761128 DOI: 10.1007/s00520-006-0086-x]

[2]   Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. Journal of Consulting and Clinical Psychology 1988; 56: 893-897 [PMID: 3204199 DOI: 10.1037//0022-006x.56.6.893]

[3]   Beck AT. An inventory for measuring depression. Archives of General Psychiatry 1961; 4: 561 [PMID: 13688369 DOI: 10.1001/archpsyc.1961.01710120031004]

[4]   Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron 2006; 52: 77-92 [PMID: 1810425 DOI: 10.1016/j.neuron.2006.09.021]

[5]   Cascinu S, Giordani P, Agostinelli R, Gasparini G, Barni S, Beretta GD, Pulita F, Iacorossi L, Gattuso D, Mare M, Munao S, Labianca R, Todeschini R, Camisa R, Cellerino R, Catalano G. Pain and its treatment in hospitalized patients with metastatic cancer. Supportive Care in Cancer 2003; 11: 587-592 [PMID: 12905055 DOI: 10.1007/s00520-003-0491-3]

[6]   Charles D Spielberger RG, Robert E Lushene, Vagg P.R, Gerard A Jacobs. Manual for the state-trait anxiety inventory. CA:Consulting Psychologists Press, 1983:

[7]   Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, Pandya KJ. Pain and its treatment in outpatients with metastatic cancer. New England Journal of Medicine 1994; 330: 592-596 [PMID: 7508092 DOI: 10.1056/nejm199403033300902]

[8]   Larue F, Colleau SM, Brasseur L, Cleeland CS. Multicentre study of cancer pain and its treatment in france. BMJ 1995; 310: 1034-1037 [PMID: 7728056 DOI: 10.1136/bmj.310.6986.1034]

[9]   Maltoni M. Opioids, pain, and fear. Annals of Oncology 2008; 19: 5-7 [PMID: DOI: 10.1093/annonc/mdm555]

[10]   Medeiros M, Oshima CT, Forones NM. Depression and anxiety in colorectal cancer patients. Journal of gastrointestinal cancer 2010; 41: 179-184 [PMID: 20180047 DOI: 10.1007/s12029-010-9132-5]

[11]   Melzack R. The mcgill pain questionnaire: Major properties and scoring methods. Pain 1975; 1: 277-299 [PMID: 1235985 DOI: 10.1016/0304-3959(75)90044-5]

[12]   Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, Meader N. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care

settings: A meta-analysis of 94 interview-based studies. The Lancet Oncology 2011; 12: 160-174 [PMID: 21251875 DOI: 10.1016/s1470-2045(11)70002-x]

[13] Mystakidou K, Mendoza T, Tsilika E, Befon S, Parpa E, Bellos G, Vlahos L, Cleeland C. Greek brief pain inventory: Validation and utility in cancer pain. Oncology 2000; 60: 35-42 [PMID: 11150906 DOI: 10.1159/000055294]

[14] Nederland IK. Richtlijn colorectaal carcinoom en colorectale levermetastasen. 2013. *First pages of the article attached at the bottom of this document

[15] Oliveira Miranda D, Soares de Lima TA, Ribeiro Azevedo L, Feres O, Ribeiro da Rocha JJ, Pereira-da-Silva G. Proinflammatory cytokines correlate with depression and anxiety in colorectal cancer patients. BioMed research international 2014; 2014: 739650 [PMID: 4182686 DOI: 10.1155/2014/739650]

[16] Palalogos Ramona AM, Loredana Balacescu, Ariana Nemes2,Robert Rajcsanyi, Tobias Jozsef, Calin Cainap, Claudia Burz. The assessment of cancer pain treatment using the pain management index in hospitalized patients with cancer.A pilot study. Journal of Radiotherapy & Medical Oncology 2012; XVII: 64-68

[17] Portenoy RK, Lesage P. Management of cancer pain. The Lancet 1999; 353: 1695-1700 [PMID: 10335806 DOI: 10.1016/s0140-6736(99)01310-0]

[18] Sabatowski R, Arens ER, Waap I, Radbruch L. Tumorschmerztherapie in deutschland. Der Schmerz 2001; 15: 241-247 [DOI: 10.1007/s004820100054]

[19] Saxena A, Mendoza T, Cleeland CS. The assessment of cancer pain in north india. Journal of Pain and Symptom Management 1999; 17: 27-41 [PMID: 9919863 DOI: 10.1016/s0885-3924(98)00104-3]

[20] Scopaz KA, Piva SR, Wisniewski S, Fitzgerald GK. Relationships of fear, anxiety, and depression with physical function in patients with knee osteoarthritis. Archives of Physical Medicine and Rehabilitation 2009; 90: 1866-1873 [PMID: 19887210 DOI: 10.1016/j.apmr.2009.06.012]

[21] Schuurhuizen CS, Braamse AM, Beekman AT, Bomhof-Roordink H, Bosmans JE, Cuijpers P, Hoogendoorn AW, Konings IR, van der Linden MH, Neefjes EC, Verheul HM, Dekker J. Screening and treatment of psychological distress in patients with metastatic colorectal cancer: Study protocol of the tes trial. BMC cancer 2015; 15: 302 [PMID: 4407474 DOI: 10.1186/s12885-015-1313-y]

[22] Simon AE, Thompson MR, Flashman K, Wardle J. Disease stage and psychosocial outcomes in colorectal cancer. Colorectal Disease 2009; 11: 19-25 [PMID: 18355377 DOI: 10.1111/j.1463-1318.2008.01501.x]

[23] Tsunoda A, Nakao K, Hiratsuka K, Yasuda N, Shibusawa M, Kusano M. Anxiety, depression and quality of life in colorectal cancer patients. Int J Clin Oncol 2005; 10: 411-417 [PMID: 16369745 DOI: 10.1007/s10147-005-0524-7]

[24] Uki J, Mendoza T, Cleeland CS, Nakamura Y, Takeda F. A brief cancer pain assessment tool in japanese. Journal of Pain and Symptom Management 1998; 16: 364-373 [PMID: 9879161 DOI: 10.1016/s0885-3924(98)00098-0]

[25] van den Beuken-van Everdingen M, de Rijke J, Kessels A, Schouten H, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: A systematic review of the past 40 years. Annals of Oncology 2007; 18: 1437-1449 [PMID: 17355955 DOI: 10.1093/annonc/mdm056]

[26] van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: A systematic review of the past 40 years. Annals of oncology : official journal of the European Society for Medical Oncology 2007; 18: 1437-1449 [PMID: 17355955 DOI: 10.1093/annonc/mdm056]

[27] Ward MM, Marx AS, Barry NN. Psychological distress and changes in the activity of systemic lupus erythematosus. Rheumatology 2002; 41: 184-188 [PMID: 11886968 DOI: 10.1093/rheumatology/41.2.184]

[28] Wells N, Murphy B, Wujcik D, Johnson R. Pain-related distress and interference with daily life of ambulatory patients with cancer with pain. Oncology Nursing Forum 2003; 30: 977-986 [PMID:14603355 DOI: 10.1188/03.onf.977-986]

[29] White KP, Nielson WR, Harth M, Ostbye T, Speechley M. Chronic widespread musculoskeletal pain with or without fibromyalgia: Psychological distress in a representative community adult sample. The Journal of rheumatology 2002; 29: 588-594 [PMID: 11908578]

[30]   Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. Psycho-oncology 2001; 10: 19-28 [PMID: 11180574 DOI: 10.1002/1099-1611(200101/02)10:1<19::AID-PON501>3.0.CO;2-6]

[31]   Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica Scandinavica 1983; 67: 361-370 [PMID: 6880820 DOI: 10.1111/j.1600-0447.1983.tb09716.x]