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Some Aspects of Psychocorrection in Oncology

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Abstract

Cancer is the second leading cause of death globally; it accounted for 9.6 million deaths worldwide in 2018 (around 15% of all deaths). Of all deaths, 1 in 4 cases is attributable to different forms of oncological diseases [1]. Meanwhile the number of survivors continues to grow, not just because of earlier detection and treatment, but also because of revolutionary new therapies. About 9 million Americans of all ages are living with a current or past diagnosis of cancer; in 2007-13 five-year survival rates for all cancers increased to 67%. For many individuals, this changes the landscape from a terminal illness to more of a chronic illness with periods of remission and exacerbation of symptoms. This perspective on neoplasms has broadened the scope of care from treating the disease alone to managing cancer-related symptoms at different stages of the disease trajectory including mental disorders. According to Holland, Alici, and Massie the prevalence of psychiatric disorders in cancer patients is over 50% [2, 3].

Life-threatening illness has recently been recognized as a stressor, but of specific nature: it is extremely complex and compounded, subtle and ambiguous [4]. Threats range from past to future: from diagnosis, implications of treatment, changes in family dynamics, uncertainty of illness progress and treatment efficacy, etc [5]. The diagnosis with cancer has a tremendous psychological impact on patients and their families, causing high levels of distress, significantly impairing psychological functions. After the disclosure of the diagnosis, most people experience intense symptoms of anxiety, depression, hopelessness, and cognitive-behavioral dysfunctions. Their condition is getting worse with emotional, social, professional, spiritual problems in addition to the multiple physical sequelae [6-10]. Moreover, treatment is associated with considerable patients' ambiguity, when they become subjected to iatrogenic physical suffering (e.g., pain, nausea, fatigue), and simultaneously get the desired hope of recovery [11].

The confrontation with a severe disease and its treatment induces high levels of uncertainty, anxiety, depression and precipitate posttraumatic stress disorder. In some cases, after approximately 2-3 weeks, distress starts to decrease. The patients try to find acceptable levels of functioning, while struggling to incorporate the event in an accommodating way into their life narratives [12-14].

Adjustment to cancer is not a unitary, single event but rather a series of ongoing coping responses to the multiple tasks associated with living with cancer. Common periods of crisis and significant challenge include the following:

- Initial diagnosis.
- Active treatment (surgery, radiation, and chemotherapy).
- Posttreatment and remission.
- Recurrence.
- Terminating curative treatment.
- Long-term survivorship.

Each of these events includes certain coping tasks, particular existential questions, many common emotional responses, and specific problems [15].

Coping refers to the specific thoughts and behaviors that patients use in their efforts to adjust [16]. One cognitive theory of coping proposes that in response to significant life events, a person asks two important questions:

- Is this event personally significant to me?
- What resources do I have to manage/control this event?

Coping strategies refer to specific cognitive and behavioral activities that use situation-specific coping efforts, such as readjusting one's daily routine or work schedule to adjust to the side effects of cancer treatment. Coping strategies comprise efforts to adjust. Among many successful coping strategies, three broad categories have been noted:

- Problem focused.
- Emotion focused.
- Meaning focused [17-19].

The process of adaptation to the diagnosis, treatment and changed life conditions follows a highly individualized trajectory over the course of illness, depending not only on medical, but also on the psychological and social facets of the disease, pre-diagnosis abilities to adjust to illness (personality and coping styles), available social

and emotional support, etc [20]. During this process, patients are presumed to draw on their resources (cognitive, psychosocial, motivational, etc.) in order to create a protective shield against the prolonged negative effects in their emotional and overall functioning [21, 22].

Cancer-related distress is frequently left unobserved, misdiagnosed and mistreated [23]. Untreated distress may significantly lower patients' quality of life and negatively impact adherence to treatment and survival [24]. The most common forms usually include adjustment disorders, major depression, delirium [3, 25-27]. The adjustment disorders are a diagnostic category, defined as reactions to an identifiable psychosocial stressor (e.g., cancer diagnosis). Such reactions are in excess of normal reactions to cancer and occur within 3 months of the onset of the stressor with a degree of psychopathology that is less severe than diagnosable mental disorders, and yet are "in excess of what would be expected" or result "in significant impairment in social or occupational functioning" [28]. Adjustment disorder is diagnosed in patients who experience maladaptive behaviors and/or moods in response to an identified stressor. The determination can be complicated in the patient with cancer, where the stressor is ongoing: diagnosis, treatment, recurrence, side effects. The maladaptive behaviors or moods include severe nervousness, worry, jitteriness, and impairment in normal functioning, such as the inability to work, attend school, or interact with others. The most common subtypes are: 1) with depressed mood, 2) with anxiety, 3) with anxiety and depressed mood, and 4) with mixed disturbance of emotions and conduct. Most patients with adjustment disorder respond to reassurance, relaxation techniques, cognitive-behavioral & mindfulness-based techniques, low doses of short-acting benzodiazepines, and patient support and education programs [29, 30].

Anxiety

Anxiety is a frequent response to threat, hence it is found in all clinical populations. Cancer is threatening, and understandably many patients are anxious in response to that threat. Investigators have found that 44% of patients with cancer reported some anxiety; 23% reported significant anxiety [31-33]. Age, gender, marital status, social class and education are not associations consistently seen with anxiety in cancer patient populations. Perhaps when the stressor is more severe, degrees of susceptibility become less important [34]. Anxiety is often manifested in individuals at various times during cancer screening, diagnosis, treatment & recurrence. It can be both adaptive and maladaptive or morbid.

Anxiety becomes maladaptive, when it is exaggerated and disproportionate related to the magnitude of the danger, or when it precludes adaptation, and becomes chronic impediment of recovery [35]. Herewith patients experience significant reductions of self-efficacy to solve the problems at hand and thus further exacerbate the experienced anxiety.

Such pathological anxiety is identified by:

1. Being out of proportion to the level of threat
2. Persistence or deterioration without intervention
3. A level of symptoms which are unacceptable regardless of the level of threat (these include recurring panic attacks, severe physical symptoms, and abnormal beliefs such as thoughts of sudden death).
4. A disruption of usual or desirable functioning.

Reactions that are more prolonged or intense can no longer be classified as adjustment disorders.

While it is clear that cancer is a threat to future health and to life, it is not a cause of disabling anxiety in the majority of patients. It does not seem that particular parts of the process of illness, investigation and treatment are predictably making most patients anxious. Instead, it may be necessary to explore the interpretations and meanings attached to events for the individual. This was observed by Lazarus, who characterized patient responses to illness in terms of the emotional elements of events; fear, anger, or sadness, and the meaning of the cancer; its identity, time-course, consequences, cause, and controllability [36].

For some patients, particularly those who have experienced episodes of intense anxiety before their cancer diagnosis, feelings of anxiety may become overwhelming. These disorders can negatively affect quality of life, a person's behavior regarding health, e.g. contribute to a delay in contacting a physician. Intrusive and unpleasant anxious thoughts, often involving recurrence of disease, death, or disability, can cause considerable disruption in concentration, decision-making, sleep. They interfere with a cancer treatment and patient's ability to function socially & emotionally, and require intervention [37].

In the case of patients diagnosed with cancer, anxious reactions may stem from different aspects (including a history of severe physical or emotional trauma and grief avoidance; they have different progress as the disease progresses in spite of treatment or as latter becomes more aggressive. In advanced cancer patients, more often experience anxiety not due to fear of death, but from fear of uncontrolled pain, being left alone, or dependency on others. The basic, existential threat of death is exacerbated by the specific threats of surgery-induced deformity, abandonment, and worries regarding the possible recurrence and aggravation of illness. Anxiety disorders may also be secondary to other aspects of the medical condition, such as certain metabolic states, hormone-secreting tumors, anxiety-producing drugs (corticosteroids, neuroleptics used as antiemetics, thyroxine, bronchodilators, beta-adrenergic stimulants, antihistamines, and benzodiazepines (paradoxical reactions are often seen in older persons), anxiety-producing conditions, disability, medication side effects (e.g. anticipatory nausea and vomiting) or pain. In other hand, the pain precipitation in anxious patients is well-known and called "vicious circle". If left untreated, anxiety may even be associated with lower survival rates from cancer [38].

Anxiety disorders are usually associated with other disorders within the emotional spectrum; such association is relatively high both in the general population and in the case of cancer patients - here a co-variance with depression ranges 0.67-0.81 [39, 40].

In this cohort mixed anxious and depressive disorders are commoner than anxiety disorders occurring alone, and therefore it has been recommended that clinicians assessing anxiety always seek co-existent depression, as treatment for depression may resolve the anxiety [41]. Such forms of comorbidity may further on aggravate the patients' situation.

Anxiety produces a number of typical symptoms and signs. Symptoms of autonomic over-activity include palpitation and sweating. Anxious behaviours such as restlessness and reassurance-seeking are a feature. Changes in thinking include apprehension, worry and poor concentration, and physical symptoms such as muscle tension or fatigue may occur. Anxiety can contribute to anorexia, nausea, vomiting and fatigue in cancer patients when they demonstrated reduction in these physical symptoms after psychotherapy [42].

The level of anxiety must be judged against the proximity of threat. For example, it is normal to experience considerable anxiety for a period of 7–10 days after receiving bad news, but as the degree of real threat varies throughout the history of the cancer, so therefore do levels of normal anxiety [43]. In certain situations too little anxiety may be as problematic for adaptation as too much, and so while thoughts about recurrence and death will be natural early after diagnosis or relapse, they are not so during a long remission, with the point of transition being difficult to ascertain. While the duration of symptoms is usually important in distinguishing abnormal anxiety the natural history of anxiety in oncology is uncertain, so this criterion is also difficult to apply. This may be because a range of definitions of abnormal anxiety have been used, and because anxiety is often labile and situational, making the onset of an episode difficult to define. Persistent anxiety may be identified quite early after diagnosis of cancer: anxiety which persists only 3 weeks after a 'bad-news consultation' is highly predictive of anxiety 6 months later. The prevalence of anxiety problems after a cancer diagnosis falls over the following years, but may not return to population levels even with curative treatment [44]. Unacceptable symptoms and disruption in functioning are often at least as useful in defining pathological anxiety in a cancer patient as other criteria. Intrusive and unpleasant anxious thoughts, often involving recurrence of disease, death, or disability, can cause considerable disruption in concentration, decision-making, sleep, and social functioning. Consequent behaviours, such as avoidance, repetitive checking of health, and seeking reassurance for transient somatic symptoms, can be disruptive for the individual and their family.

In psycho-oncological settings, the screening of anxiety usually is undertaken in three different ways:

1. Single symptom assessment (direct questions, or assessment of non-verbal cues of anxiety),
2. Multiple symptom assessment (e.g., screening with anxiety scales as Hospital Anxiety and Depression Questionnaire, State and Trait Anxiety Inventory), and
3. Assessment of clinical syndrome (assessment of clusters of symptoms, which constitute specific syndromes as generalized anxiety disorder, panic disorder, phobias, etc.) [34].

Having identified that an individual has problems with anxiety, there is a need to intervene either within cancer care or by referring for specialist treatment.

Treatment for anxiety begins by giving the patient adequate information and support. Data need to be tailored to the wishes of the individual. Knowledge achieves reduction in anxiety, when it is tailored to an understanding of the meaning of events to the patient. Poor or incomplete information can generate mistrust of medical staff. Developing coping strategies such as the patient viewing his or her cancer from the perspective of a problem to be solved, obtaining enough information in order to fully understand his or her disease and treatment options, and utilizing available resources and support systems, can help to relieve anxiety. Medications may be used alone or in combination with these techniques.

Treatment depends on how the anxiety is affecting daily life for the patient. Anxiety that is caused by pain or another medical condition, a specific type of tumor, or as a side effect of medication (such as steroids), is usually controlled by treating the underlying cause. Notably there was no difference in effectiveness of such treatments between patients with metastatic and those with better-prognosis disease.

Treatments of cancer-related anxiety include elements of psycho-education, in which patients are offered (verbally or in a written format) practical knowledge regarding the implications of the illness, treatment process, medical system, availability of support groups etc [34]. Psychologic approaches include combinations of cognitive-behavioral psychotherapeutic techniques, insight-oriented psychotherapy, crisis intervention, couple and family therapy, group therapy, self-help groups. Patients may benefit from other treatment options for anxiety, including hypnosis, and relaxation techniques such as guided imagery (a form of focused concentration on mental images to assist in stress management), or biofeedback. These approaches used to treat anxiety symptoms that are associated with painful procedures, pain syndromes, crisis situations, anticipatory fears, and depressive syndromes. Patients are not deprived of hope by information; they do not necessarily ask for the further information they want, so many retain lay perceptions that are "worse than the facts" [43]. Effective communication skills are central to information giving, with substantial correlation between anxiety and poor communication with the medical team. Oncologists are often asked to reassure anxious patients that their experienced symptoms are not due to worsening of the cancer. However, even in the absence of progression of the cancer after appropriate investigation, well-meaning simple reassurance may inadvertently worsen anxiety. A cognitive model of this problem has been suggested, which has the potential advantage of allowing oncologists to intervene specifically to help some anxious patients. The model identifies a group of beliefs and behaviours characteristic of patients who are anxious about their health:

- Beliefs: Tending to interpret everyday bodily symptoms as indicative of serious disease
- Concerns: Health worry and preoccupation, fear of serious illness, and of death. This can be intrusive and difficult to control
- Behaviours: Reassurance-seeking, including seeking medical consultation [44].

After a cancer diagnosis, patients learn to monitor their bodies for symptoms of relapse, and interpret their symptoms. Health anxiety may be seen as a maladaptive pattern of such monitoring.

Cognitive therapy aiming to modify patients distorted thought related to the target event and their implications, thus ameliorating symptoms of anxiety has also proved to be of variable effectiveness [45, 46]. More effective proved to the problem-solving therapy, a refined variant of cognitive therapy. In these interventions are assisted to optimize their coping skills and their abilities to solve

more effectively the problems they encounter. This form of intervention was found to effectively reduce distress (measured with the Brief Symptom Inventory), but yielded no significant reduction in anxiety per se [47-57]. Exercises involving relaxation also contribute to the reduction of tension and anxiety in cancer patients, especially if these exercises are adapted to the specific needs of the patient [58].

There are several pharmacological interventions of demonstrated efficacy:
Short-acting benzodiazepine (sbd), such as alprazolam; long-acting benzodiazepine, such as diazepam (useful to manage recurrent symptoms after a course of sbd); beta-blockers; tricyclic antidepressants, such as imipramin; selective serotonin reuptake inhibitors, such as paroxetin (less toxic than tricyclics); neuroleptics, such as haloperidol - adjunct to benzodiazepines. The medicinal agents are chosen with the consideration of the presence or absence of specific psychiatric or medical comorbidities: pain, depressive symptoms, hot flashes, medications' side effects etc.

Depression

Among the nosological forms of comorbid mental pathology in cancer patients, affective disorders (depression & anxiety) predominate and have been the most studied ones [3, 59, 60]. This predomination is very distinct in long-term cancer survivors. The reported prevalence of depressive symptoms in cancer has been variable, depending on cancer type and stage, timing and method of assessment, diagnostic criteria applied, and demographics of the population studied. Higher rates of depressive symptoms in cancer have been found toward the end of life and in specific cancers, such as lung, pancreatic, gastric, and oropharyngeal ones [20]. Although depression has been reported to be 2 to 3 times more common in women than in men in the general population, this disparity has not been observed in cancer, perhaps because the burden of disease may be equally distributed by sex. Receiving a deadly diagnosis, going through treatment protocols, interruption of life plans, learning to live with limitations, changes in lifestyle, social role, body image & self-esteem and financial & legal concerns can cause depression in many patients, as can side effects from the treatment itself. Cancer increase patients' susceptibility to depression in several ways. First, a reaction to a potentially fatal diagnosis and the forthcoming deterioration of health status constitute a risk factor for depression; second, treatment with immune response modifiers and chemotherapy regimens, as well as metabolic and endocrine alterations, chronic pain and extensive surgical interventions, may represent additional contributing factors [61, 62]. Still, not everyone with cancer becomes depressed. Normally, a patient's initial emotional response to the crises faced during cancer is brief, extending over several days to weeks, and may include feelings of denial, disbelief, despair, sadness and grief.

Depressive symptoms occur on a wide continuum, from reactions of normal intensity and duration (usually nonpathologic sadness), to minor or subthreshold depression in the middle, and major disorders and somatic consequences of the illness and its treatment at the more severe end of the spectrum [63]. More vigorous symptoms of depression are of clinical concern because of their high correlation with marked distress, more prolonged hospital stays, physical disorders, poorer treatment compliance & adherence to therapy, disability, lower quality of life, earlier admission to inpatient or hospice care increased desire for hastened death, and completed suicide [64, 65]. According to meta-analysis, depressed patients are three times more likely to not adhere to treatment than the non-depressed patients [66].

If untreated, depression has been shown to negatively influence the underlying cellular and molecular processes that facilitate the progression of cancer. Pretreatment depressive symptoms (DS) in cancer patients worsen survival. There was also found that those with persistent/recurrent/late DS have higher risk of earlier death compared to the reference group of people who never experienced them during the first year, while people who recovered from DS had the same risk. A meta-analysis revealed that minor or major depression increases the rate of mortality by up to 39%; in addition, patients displaying even a few depressive symptoms may be at a 25% increased risk of mortality. The effects of depression on mortality may differ by cancer site, being highest in people with lung and gastrointestinal cancer, and lower in those with genitourinary and skin cancer [51].

Emergence of depression in cancer patients may be understood as a final common pathway resulting from the interaction of multiple disease-related, individual, and psychosocial factors. A crucial question remains though still unanswered – the degree to which depression rates are determined by the pathophysiological effects of the tumor and the effects of the treatment [1].

The pathophysiology of cancer-related depression probably encompasses many mechanisms. A study of patients with advanced metastatic cancer showed that both plasma interleukin-6 concentrations and hypothalamic-pituitary-adrenal axis dysfunction were markedly higher in patients with clinical depression. There is mounting evidence that tumor cell burden and treatment-induced tissue destruction, which release pro-inflammatory cytokines that alter neurotransmitter and neuroendocrine function, may contribute to depressive symptoms in cancer patients with, captured under the rubric of cytokine-induced depression.

Major depression refers to a syndrome characterized by at least five symptoms present for at least 2 weeks, one of which is depressed mood or anhedonia. The other symptoms include appetite or sleep disturbance, psychomotor agitation or retardation, decreased energy, feelings of worthlessness or guilt, difficulty concentrating, or suicidal ideation. Minor depression is diagnosed when only 2 to 4 of these symptoms are present for at least 2 weeks; dysthymia, when 3 to 4 symptoms are present. The most common form of depressive symptomatology in people with cancer is an adjustment disorder with depressed mood, sometimes referred to as reactive depression which may be under-recognized and undertreated. This disorder is manifested when a person has a dysphoric mood that is accompanied by the inability to perform usual activities. The symptoms appear to be prolonged and in excess of a normal and expected reaction to a stressor but do not meet the criteria for a major depressive episode. Many patients with subthreshold or minor depression do not progress to major depression. Many symptoms of cancer and its treatment, such as fatigue, anorexia, insomnia, and cognitive impairment, overlap with those of depression. Cancer-related depression can exist before the diagnosis of cancer or may develop after the cancer is identified. While there is no evidence to support a causal role for depression in cancer, it may impact the course of the disease and a person's ability to participate in treatment.

Evaluation of depression in people with cancer should include careful assessment of symptoms, treatment effects, laboratory data results, physical status, and mental status. Assessment methods include self-report measures, screening instruments, clinical interviews. Among the physically ill, in general, instruments used to measure depression have not been shown to be more clinically useful than an interview and a thorough examination of mental status.

The Diagnostic and Statistical Manual of Mental Disorders is one of the most common tools used to diagnose depression, particularly among non-terminally ill patients. It outlines somatic complaints associated with the condition, such as changes in appetite, sleep disturbance, energy, and difficulty thinking or concentrating.
The diagnosis is difficult due to the problems inherent in distinguishing biological or physical signs of depression (changes in weight or appetite, fatigue or loss of energy, and/or sleep) from symptoms of illness or toxic side effects of treatment. Depressive disorders are often not recognized in patients with cancer because the somatic symptoms of depression—including changes in appetite, energy, and/or sleep—may be attributed to normal cancer-related changes or to cancer treatment side effects. This is particularly true of individuals who are receiving active treatment or those with advanced disease. In addition, these somatic signs overlap with the changes seen in cancer patients who are not depressed [21].

It highlights the special importance of assessing for signs of depression. This can be done by conducting an interview with the patient. Cognitive symptoms may express themselves as repeated and ruminative thoughts such as "I brought this on myself," "God is punishing me," and as fatalistic expectations concerning prognosis, despite realistic evidence to the contrary. The other cognitive disorders such as guilt, worthlessness, hopelessness, thoughts of suicide, and loss of pleasure in activities are probably the most useful in diagnosing depression in people with cancer. Clinicians often rely on the cognitive symptoms than the physical/somatic signs when making a diagnosis of depression in patients with advanced disease. In this cohort atypical depressive symptoms such as anxiety, despair, inner restlessness and social withdrawal, might be more frequent, and need to be taken into account when depressive symptoms are assessed.

Some patients will not volunteer such thinking but will respond to brief inquiries on this subject, for example "Do you find yourself ever thinking I brought this on myself, God is punishing me? How often? Only a few times a week, or all the time?" Another example is to say, "Please grade your mood during the past week by assigning it a score from 0 to 100, with a score of 100 representing your usual relaxed mood." A score of 60 is considered a passing grade. Simply asking the patient whether he or she is depressed may improve the identification of depression. It is possible for a nurse to ask such question without becoming engaged in providing counseling themselves.

Suicidal statements may range from an offhand comment resulting from frustration or disgust with a treatment course: "If I have to have one more bone marrow aspiration this year, I'll jump out the window," to a reflection of significant despair and an emergent situation: "I can no longer bear what this disease is doing to all of us, and I am going to kill myself." Exploring the seriousness of the thoughts is imperative. If the suicidal thoughts are believed to be serious, a referral to a psychiatrist or psychologist should be made immediately and attention should be given to the patient's safety. Individuals should be referred for a psychiatric consultation for the following reasons:

1. A primary care physician or oncologist does not feel competent treating the patient for depression because of specific clinical features in the presentation (i.e., if prominent suicidal tendencies are present).
2. The depressive symptoms treated by the primary physician are resistant to pharmacologic interventions after 2 to 4 weeks of intervention.
3. The depressive symptoms are worsening rather than improving.
4. Initiating treatment with antidepressant drugs, titrating drug doses, or continuing treatment is interrupted or made problematic by adverse effects attributable to the medication.
5. The depressive symptoms are interfering with the patient's ability to be cooperative with medical treatment.

A critical part of cancer care is the recognition of the levels of depression present and determination of the appropriate level of intervention, ranging from brief counseling or support groups to medication and/or psychotherapy. At least one half of all people diagnosed with cancer will successfully adapt. Markers of adaptation include maintaining active involvement in daily life; minimizing the disruptions caused by the illness to one's life roles (e.g., spouse, parent, employee); regulating the normal emotional reactions to the illness; and managing sense of burden to others, feelings of hopelessness, helplessness, worthlessness, and/or guilt.

The treatment of depression in these patients should address not only the depressive symptoms but also the disease-related & psychosocial factors that contribute to the emergence of depression in this context. These include the treatment of pain and other distressing physical symptoms, the relationship with oncologists and other medical care providers, the social support system, and the individual experience of illness. For depression in such persons to alleviate both psychosocial and pharmacological interventions are developed. Typically, antidepressant medication is most effective for severe depression, whereas psychotherapy is recommended for both mild and severe cases of depression.

Psychologic interventions include not only interventions delivered by specialists in psychosocial oncology but also the support provided by medical caregivers as part of cancer care. This support contributes relieving traumatic stress in cancer patients. Recently diagnosed patients with mild to moderate depression may benefit from psychoeducation, cognitive behavioral therapy, relaxation strategies, and problem-solving approaches. Patients who have more advanced disease may benefit from supportive-expressive psychotherapy that focuses on processing fears associated with death and other existential concerns.

Special note-worthy intervention is dignity therapy. The term "dignity" provides an overarching framework that may conserve or bolster the dignity of dying patients.This approach will be outlined in Supplement. Pharmacotherapy for depression in patients with advanced cancer should be guided by a focus on symptom reduction, irrespective of whether the patient meets the diagnostic criteria for major depression. European guidelines on

the management of depression in palliative cancer care recommends antidepressant intake not only in major depression but also in mild depression, if symptoms persist after first-line treatments have failed.

Amongst antidepressants, many different agents are available, including tricyclics (TCAs), monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors and other newer agents, such as agomelatine, mirtazapine, reboxetine, bupropion. SSRIs are not more effective than TCAs but are better tolerated and safer in overdose than TCAs. Few evidence-based meta-analyses have shown mianserin for the treatment of depressive symptoms and paroxetine for the prevention of new episodes to be superior compared with other SSRIs.

The optimal antidepressant for specific patients can be determined by each patient's depressive symptom profile and potential dual benefit for depression and cancer-related symptoms such as anorexia, insomnia, fatigue, neuropathic pain, and hot flashes. Here special attention is paid to duloxetine, venlafaxine, mirtazapine. Because of both their adverse effect profiles and risk for lethality in overdose, tricyclic/heterocyclic antidepressants, monoamine oxidase inhibitors, and reversible inhibitors of monoamine oxidase A are rarely used in patients with cancer.

Delirium

Cancer patients often have delirium particularly ones with far-advanced disease. Delirium has been defined as a disorder of global cerebral dysfunction characterized by disordered awareness, attention, and cognition. The term acute confusional state has also been used to describe this syndrome which is, in addition, associated with behavioral manifestations. Occurrence rates range from 28% to 48% in patients with advanced cancer on admission to hospital or hospice, and approximately 90% of these patients will experience delirium in the hours to days before death, the condition sometimes referred to as terminal restlessness probably represents a terminal delirium. Less than 10% of patients with a PS of 0–2 were diagnosed as having delirium, as opposed to more than 40% of patients with a PS of ≥3. The disease is more often diagnosed in men & in younger patients than in women & older patients.

The core clinical criteria for this diagnosis:

- A disturbance of consciousness with reduced clarity of awareness and attention deficit.
- Other cognitive or perceptual disturbances.
- Acuity of onset (hours to days) and fluctuation over the course of the day.
- The presence of an underlying cause such as a general medical condition (e.g., hypoxia or electrolyte disturbance), medication, a combination of etiologies, or indeterminate etiology.

Other associated noncore clinical criteria features include sleep-wake cycle disturbance, delusions, emotional liability, and disturbance of psychomotor activity. The latter forms the basis of classifying delirium into three different subtypes:

1. Hypoactive.
2. Hyperactive.
3. Mixed, with both hypoactive and hyperactive features.

The delirium is multifactorial, especially in the setting of advanced cancer. The reasons include

1. The direct impact of cancer on the central nervous system (CNS). Correlation between levels of circulating cytokines at diagnosis and specific types of cognitive dysfunction.
2. Indirect CNS effects related to systemic complications of cancer such as organ failure (e.g., hepatic or renal failure), metabolic or electrolyte disturbance (e.g., hypoglycemia, hypercalcemia, hyponatremia, or dehydration), infection, and paraneoplastic syndromes.

Despite the very limited systematic study of risk factors for delirium in patients with cancer, risk factors have been identified in general medical patients (some of them with cancer) and include severe illness, level of comorbidity, advanced age, prior dementia, hypoalbuminemia, infection, azotemia, and psychoactive medications. The diagnosis of delirium should be considered in any patient with cancer demonstrating an acute onset (hours to days) of agitation or uncooperative behavior, personality change, impaired cognitive functioning, altered attention span, fluctuating level of consciousness, or uncharacteristic anxiety or depression. This diagnosis is frequently missed and poorly documented.

Delirium clearly has a recognized association with the dying phase, but many episodes of delirium are reversible; such reversal is consistent with the goals of care; therefore, the standard management approach in these patients is to search for and treat the reversible precipitants of delirium. Care includes stopping unnecessary medications, reversing metabolic abnormalities, treating the symptoms of delirium, and providing a safe environment. Agents known to cause delirium include corticosteroids, CT agents, biological response modifiers, antidepressants, benzodiazepines, opioids, and anticholinergic agents. The neuroleptic haloperidol is still considered the drug of choice for the treatment of delirium in the patients with cancer. It has a low incidence of cardiovascular and anticholinergic effects. Consensus guidelines recommended initial doses in the range of 1 to 2 mg every 2 to 4 hours as needed (to 4 mg orally, intravenously, or subcutaneously) and lower starting doses, such as 0.5 mg every 4 hours as needed, in elderly patients.

Risperidone is an atypical antipsychotic with fewer extrapyramidal side effects than haloperidol. It's available in oral tablet and liquid formulations; dosing begins at 1 to 2 mg per day in two divided daily doses that are titrated, if necessary, to a total daily dose of 4 to 6 mg per day. Therapeutic intervention results in delirium reversal, or at least improvement, in 30% to 75% of episodes. In intractable cases, palliative sedation may be warranted. Safety measures include protecting patients from accidents or self-injury while they are restless or agitated. The use of restraints is controversial; other strategies include having family members or sitters at the bedside to prevent harm.

Dementia is a progressive neurodegenerative condition that increases with age. It's a syndrome – usually of a chronic or progressive nature – in which there is deterioration in cognitive function (i.e. the ability to process thought) beyond what might be expected from normal ageing. The impairment in cognitive function is commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behavior, or motivation. Dementia is described as a disorder with memory impairment and at least one other symptom from another cognitive domain: aphasia,

apraxia, agnosia or disturbances in executive functioning accompanied by impairment in social and occupational function. It affects memory. thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not affected. Dementia results from a variety of diseases and injuries that primarily or secondarily affect the brain, such as Alzheimer's disease or stroke. The course is characterized by gradual onset and continuing cognitive decline. The symptoms of dementia can be clustered under three dementia neuropsychological, neuropsychiatric and executive function features.

Age is a risk factor for most cancers and estimates suggest that by 2030, 70% of all cancers will occur in elderly people. Given that both cancer and dementia are seen as diseases of elderly people, the expectation is that there will be a significant overlap of the two conditions. However, there appears to be a disconnect between the prevalence rates of the two conditions occurring together. Population-based cohort studies report lower rates of dementia in cancer survivors. The converse is also true, with lower rates of cancer in people with dementia, as compared with cognitively intact matched controls. One possible explanation is underdiagnosis of cancer. Individuals with dementia tend to under-report symptoms, such as gastrointestinal discomfort, joint pain and vision problems, which leads to delays in medical attention being sought. A definitive diagnosis of dementia in physically unwell patients with a single assessment poses challenges and follow-up assessment should be arranged. The Mini-Mental State Examination is the most widely used screening tool for dementia. It might be used as a screen for all individuals aged over 65 years, with scores under 27 triggering a referral for further screening, including neuropsychological testing.

The most common subtypes of dementia are Alzheimer's disease, VaD, mixed Alzheimer's and VaD, dementia with Lewy bodies and fronto–temporal dementia. Patients with Alzheimer's and VaD present with prominent memory impairment, initially affecting their recent memories. Patients with dementia with Lewy bodies present with prominent hallucinations, falls, a fluctuant pattern of cognitive impairment and are very sensitive to neuroleptic medication. Patients with fronto–temporal dementia present with prominent language impairments (temporal variant) or personality change and behavioral problems (behavioral variant). While on the subject of stages of dementia, usually 3 ones are called: early, middle and late. Pre-existing dementia diagnoses were associated with high mortality, mostly from non-cancer causes. Life expectancy in dementia has a bearing on clinical decision-making. Recent studies have found that survival times of patients with dementia are shorter than previously reported, with both clinicians and family members overestimating life expectancy in the patient with dementia. In dementia, the very stressful diagnosis of cancer is further complicated by the fact that the patient might not be able to fully understand the nature of the disease, the prognosis, and the risks and benefits associated with treatment.

Cognitive disorders are often multifactorial, especially in the setting of advanced cancer. General etiologic factors include the following

1. Direct effects of cancer on the central nervous system. There was found a correlation between levels of circulating cytokines at diagnosis and specific types of cognitive dysfunction. Higher levels of IL-6 associate with poorer executive function, higher levels of IL-8 correlated with improved memory
2. Indirect CNS effects related to systemic complications of cancer such as organ failure, metabolic or electrolyte disturbance, infection, and paraneoplastic syndromes. Exogenous substances such as the wide variety of medications and treatments used in these patients, including most of the commonly used chemotherapeutic agents, glucocorticoids, and especially psychoactive agents such as opioid analgesics, antidepressants, benzodiazepines, antihistamines, and other sedating agents. The question about cancer treatment leading to dementia has been studied and the results in published literature have been mixed – the association has not been borne out by a large population-based study.

Given that age is an important risk factor for cognitive impairment, older adults are much more likely to suffer cognitive impairments with treatment. Evidence from histopathological studies seems to support this. A prevalence of the cognitive impairment is best studied in breast cancer patients. During active treatments, this value proved to reach 75%. These women with such impairment are more likely to have high level of psychologic distress suggesting a relationship between two nosologic forms as it's well-known for other components of both physical and mental health.

To assess cognitive impairment, neuropsychological tests and self-reports are commonly used. Diagnosis is based ultimately on a clinical evaluation determining cognitive function and functional status and not solely on a specific test score. The correct diagnosis is necessary because this impairment becomes increasingly common as individuals age and is associated with an increased risk of progression to dementia. We are talking about a pathologic state rather than normal cognitive aging. An accurate diagnosis is important in order to assess for reversible causes of cognitive impairment, to help patients and families understand the cause of their cognitive concerns. Timely & precise diagnosis and appropriate treatment of comorbid mental disorders is required in an effort not only to increase quality of life but also to reduce adverse effects on cancer course, length of hospital stay, improve treatment adherence and efficacy, and possibly prognosis & survival.

Supplement

For patients facing end-of-life unique supporting approach was developed to relieve psychosocial and existential distress, it's called Dignity Therapy. Prior studies of dignity have shown a strong association between an undermining of dignity and depression, anxiety, desire for death, hopelessness, feeling of being a burden on others, and overall poorer quality of life. Patients deem a sense of spiritual peace, relieving burden, and strengthening relationships with loved ones among the most important facets of end-of-life care. There was suggested that meaning, or a paucity of meaning, defines the essence of existential distress. An empirical model of dignity in the terminally ill has permitted to obtain framework of questions which provides the basic content of the therapeutic process (68, 70). These conversations are designed to accommodate the patient's needs and choices regarding what he/she specifically wishes to address. To decrease suffering, enhance quality of life, and bolster a sense of meaning, purpose, and dignity, patients are offered the opportunity to address issues that matter most to them or speak to things they would most want remembered. Dignity Therapy (DT) is audio-recorded and transcribed, with an edited version of the transcript returned to patients. In randomized controlled trial DT

was compared with standard supportive approach, the former proving superior in lessening distress and enhancing end-of-life experience. Improvement of measures of depression, will to live and quality of life were observed. Persons with depressed mood and suffering seemed to be particularly responsive from DT. This is also true for ones reporting more initial psychosocial despair and less satisfaction with pain relief before the intervention - the latter were more likely to report that DT yielded an increased sense of purpose. 72% reported that it heightened the meaning of life for the ones.

Patients usually told about DT: "It really helped me remember who I am". Symptomatic relief of distress is an important goal of psychotherapeutic treatment. This intervention is not only offered to alleviate distress, but also as a means of preventing distress, promoting well-being and establishing a sense of personal meaning and life purpose. Psychotherapeutic support helps patients face disappointments, process the reality of leaving behind loved ones; deal with feelings of sadness, loss, isolation and a damaged sense of identity and personal value. It can also help to consider personal priorities regarding relationships, religious and spiritual beliefs, and deal with the urgency of resolving conflicts or achieve personally meaningful goals [67-71].

There are few interventions specifically designed to lessen the suffering or existential distress that often accompanies patients toward the end of life. The rationale of most techniques is to make the sufferer less aware of his or her suffering. As such, they offer the equivalent of emotional analgesia without necessarily addressing the source or cause of the underlying psychic pain. Unlike most other symptom-focused approaches, the beneficial effects of DT reside in being able to bolster a sense of meaning and purpose while reinforcing a continued sense of worth. The beneficial effects were obtained irrespective of whether patients indicated initial significant. psychosocial/existential distress. 81% of patients felt that DT had helped, or would be of help to, their families and that this perception was related to a heightened sense of purpose and meaning along with a diminished sense of suffering and heightened will to live. Although quality of life and sense of well-being inevitably deteriorate as physical decline ensues, suffering, depression, and sense of dignity (all facets of the patient's internal psychological and spiritual life) may have a resilience, or the capacity to improve, independent of bodily deterioration. The beneficial effects of DT are associated with an enhanced sense of meaning and purpose, both of which are intertwined with a diminished sense of suffering, lessening desire for death, and increased will to live.

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References

1. Massie MJ, Greenberg DB (2005) Oncology. In J. L. Levenson (Ed.), Textbook of psychosomatic medicine Arlington, VA: American Psychiatric Publishing, Inc 2005: 517-534.
2. Holland JC, Alici Y (2010) Management of distress in cancer patients. The Journal of Supportive Oncology 8: 4-12.
3. Massie MJ (2004) Prevalence of depression in patients with cancer. Journal of National Cancer Institute Monographs 32: 57-71.
4. Hou WK, Law CC, Yin J, Fu YT (2010) Resource loss, resource gain, and psychological resilience and dysfunction following cancer diagnosis: a growth mixture modeling approach. *Health Psychology* 29: 484-495.
5. Hou WK, Lam WWT, Fielding R (2009) Adaptation process and psychosocial resources of Chinese colorectal cancer patients undergoing adjuvant treatment: A qualitative analysis. *Psycho-Oncology* 18: 936-944.
6. Aspinwall LG, MacNamara A (2005) Taking positive changes seriously: Toward a positive psychology of cancer survivorship and resilience. Cancer 104: 2549-2556.
7. Costanzo ES, Ryff CD, Singer BH (2009) Psychosocial adjustment among cancer survivors: Findings from a national survey of health and well-being. Health Psychology 28: 147-156.
8. Coughlin SS (2008) Surviving cancer or other serious illness: A review of individual and community resources. CA: A Cancer Journal for Clinicians 58: 60-64.
9. Stanton AL, Revenson TA, Tennen H (2007) Health psychology: Psychological adjustment to chronic disease. Annual Review of Psychology 58: 565-592.
10. Kangas M, Henry JL, Bryant RA (2002) Posttraumatic stress disorder following cancer: A conceptual and empirical review. Clinical Psychology Review 22: 499-524.
11. Weeks JC, Cook EF, O'Day SJ, Petersen LM, Wenger N, et al. (1998) Relationship between cancer patients' predictions of prognosis and their treatment preferences. *Journal of the American Medical Association* 279: 1709-1714.
12. Sadock Sadock Ruiz (2009) Kaplan & Sadock's Comprehensive textbook of psychiatry. Philadelphia, PA: Lippinkott Williams and Wilkins.
13. Fallowfield LJ, Ratcliffe D, Jenkins V, Saul J (2001) Psychiatric morbidity and its recognition by doctors in patients with cancer. British Journal of Cancer 84: 1011-1015.
14. McDaniel Musselman, Porter Reed, Nemeroff (1995) Depression in patients with cancer. Diagnosis, biology, and treatment. Archives of General Psychiatry 52: 89-99.
15. Adjustment to Cancer: Anxiety and Distress. http://www.cancer.gov
16. Folkman S, Greer S (2000) Promoting psychological well-being in the face of serious illness: when theory, research and practice inform each other. Psychooncology 9: 11-19.
17. Lazarus RS, Folkman S (1978) Stress, Appraisal, and Coping. New York, NY: Springer Publishing Co.
18. Pearlin LI, Schooler C (1978) The structure of coping. J Health Soc Behav 19: 2-21.
19. Ahmad MM, Musil CM, Zauszniewski JA, Martin I Resnick (2005) Prostate cancer: appraisal, coping, and health status. J Gerontol Nurs 31: 34-43.
20. Boyd AD, Riba M (2007) Depression and pancreatic cancer. J Natl Compr Canc Netw 5: 113-116.
21. Heckhausen J, Wrosch C, Schulz R (2010) A motivational theory of life-span development. Psychological Review 117: 32-60.

22. Diener E, Lucas RE, Scollon CN (2006) Beyond the hedonic treadmill: Revising the adaptation theory of well-being. *American Psychologist* 61: 305-314.

23. Reich M, Lesur ĆA, Perdrizet-Chevallier ĆC (2008) Depression, quality of life and breast cancer: A review of the literature. Breast Cancer Research Treatment 110: 9-1723

24. Somerset W, Stout SC, Miller AH, Musselman D (2004) Breast cancer and depression. Oncology 18: 1021-1034.

25. Breitbart W, Alici Y (2008) Agitation and delirium at the end of life: We couldn't manage him. JAMA 300: 2898-2910.

26. Fleishman S, Lesco L, Breitbart WS (1993) Treatment of organic mental disorders in cancer patients. In W. S. Breitbart, & J. C. Holland (Eds.), Psychiatric aspects of symptom management in cancer patients 1993: 23-47.

27. American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Association.

28. Forester B, Kornfeld DS, Fleiss JL, Thompson S (1993) Group psychotherapy during radiotherapy: effects on emotional and physical distress. Am J Psychiatry 150: 1700-1706.

29. Jevne RF (1990) Looking back to look ahead: a retrospective study of referrals to a cancer counseling service. Int J Adv Couns 13: 61-72.

30. Breitbart W (1995) Identifying patients at risk for, and treatment of major psychiatric complications of cancer. Support Care Cancer 3: 45-60.

31. Stark D, Kiely M, Smith A (2002) Anxiety disorders in cancer patients: their nature, associations, and relation to quality of life. J Clin Oncol 20: 3137-3148.

32. Schag CA, Heinrich RL (1989) Anxiety in medical situations: adult cancer patients. J Clin Psychol 45: 20-27.

33. Noyes RJ, Holt C, Massie M (1998) Anxiety disorders. In Psycho-oncology, Holland JC (ed) pp 548–563. New York: Oxford University Press

34. Levin TT, Alici Y (2010) Anxiety disorders. In J. C. Holland, W. S. Breitbart, P. B. Jacobsen, M. S. Lederberg, M. J. Loscalzo, R. S. McCorkle (Eds.), *Psycho-oncology* 2010: 324-331.

35. Lazarus RS (1993) Coping theory and research – past, present, and future. Psychosom Med 55: 234-247.

36. Razavi D, Stiefel F (1994) Common psychiatric disorders in cancer patients. I. Adjustment disorders and depressive disorders. Support Care Cancer 2: 223-232.

37. Sirois F (1993) Psychosis as a mode of exitus in a cancer patient. J Palliat Care 9: 16-18.

38. Teunissen SC, de Graeff A, Voest EE, de Haes JC (2007) Are anxiety and depressed mood related to physical symptom burden? A study in hospitalized advanced cancer patients. *Palliative Medicine* 21: 341-346.

39. Wilson KG, Chochinov HM, Skirko MG, Allard P, Chary S, et al. (2007) Depression and anxiety disorders in palliative cancer care. *Journal of Pain Symptom Management* 33: 118-129.

40. Wise MG, Rieck SO (1993) Diagnostic considerations and treatment approaches to underlying anxiety in the medically ill. J Clin Psychiatry 54: 22-26.

41. Forester B, Kornfeld DS, Fleiss JL, Thompson S (1993) Group psychotherapy during radiotherapy: effects on emotional and physical distress. Am J Psychiatry 150: 1700-1706.

42. Holland JC (1989) Anxiety and cancer: the patient and the family. J Clin Psychiatry 50: 20-25.

43. Fallowfield LJ, Hall A, Maguire P, Baum M, A'Hern RP (1994) Psychological effects of being offered choice of surgery for breast cancer. BMJ 309: 448.

44. DPH Stark, A House (2000) Anxiety in cancer patients. British Journal of Cancer 83: 1261-1267.

45. Osborn RL, Demoncada AC, Feuerstein M (2006) Psychosocial interventions for depression, anxiety, and quality of life in cancer survivors: meta-analyses. International Journal of Psychiatry Medicine 36: 13-34.

46. Uitterhoeve RJ, Vernooy M, Litjens M, Potting K, Bensing J, et al. (2004) Psychosocial interventions for patients with advanced cancer - A systematic review of the literature. British Journal of Cancer 91: 1050-1062.

47. Nezu AM, Nezu CM, Felgoise S, McClure KS, Houts PS (2003) Project Genesis: assessing the efficacy of problem-solving therapy for distressed adult cancer patients. Journal of Consulting and Clinical Psychology 71: 1036-1048.

48. Jacobsen PB, Meade CD, Stein KD, Chirikos TN, Small BJ, et al. (2002) Efficacy and costs of two forms of stress management training for cancer patients undergoing chemotherapy. Journal of Clinical Oncology 20: 2851-2862.

49. Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, et al. (2011) Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: A meta-analysis of 94 interview-based studies. Lancet 12: 160-174.

50. Honda K, Goodwin RD (2004) Cancer and mental disorders in a national community sample: Findings from the National Comorbidity Survey. Psychother Psychosom 73: 235-242.

51. Irwin MR (2013) Depression and insomnia in cancer: prevalence, risk factors, and effects on cancer outcomes. Current Psychiatry Reports 15: 404.

52. Onitilo AA, Nietert PJ, Egede LE (2006) Effect of depression on all-cause mortality in adults with cancer and differential effects by cancer site. General Hospital Psychiatry 28: 396-402.

53. Faller H, Bülzebruck H (2002) Coping and survival in lung cancer: A 10-year followup. American Journal of Psychiatry 159: 2105-2107.

54. Newport DJ, Nemeroff CB (1998) Assessment and treatment of depression in the cancer patient. Journal of Psychosomatic Research 45: 215-237.

55. DiMatteo MR, Lepper HS, Croghan TW (2000) Depression is a risk factor for noncompliance with medical treatment: a meta-analysis of the effects of anxiety and depression on patient adherence. Archives of International Medicine 160: 2101-2107.

56. Femke Jansen, Irma M Verdonck-de Leeuw, Pim Cuijpers, C René Leemans, Tim Waterboer, et al. (2018) Depressive symptoms in relation to overall survival in people with head and neck cancer: A longitudinal cohort study. Psychooncology 27: 2245-2256.

57. Sullivan DR, Forsberg CW, Ganzini L, David H Au, Michael K Gould, et al. (2016) Longitudinal changes in depression symptoms and survival among patients with lung Cancer: A National Cohort Assessment. J Clin Oncol 34: 3984-3991.

58. Pirl WF (2010) Instruments in psycho-oncology. In J. C. Holland, W. S. Breitbart, P. B. Jacobsen, M. S. Lederberg, M. J. Loscalzo, R. S. McCorkle (Eds.), Psychooncology (2nd Ed.) (pp. 119-130). Oxford: Oxford University Press.

59. Trask PC (2004) Assessment of depression in cancer patients. Journal of the National Cancer Institute Monographs 32: 80-92.

60. Satin JR, Linden W, Phillips MJ (2009) Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. Cancer 115: 5349-5361.

61. Brenne E, Loge JH, Kaasa S, Heitzer E, Knudsen AK, et al. (2013) Depressed patients with incurable cancer: which depressive symptoms do they experience?. Palliative and Supportive Care 11: 491-500.

62. Ebtesam Ahmed (2019) Antidepressants in Patients with Advanced Cancer: When They're Warranted and How to Choose Therapy. Oncology (Williston Park) 33: 62-68.

63. Li M, Fitzgerald P, Rodin G (2012) Evidence-based treatment of depression in patients with cancer. J Clin Oncol 30: 1187-1196.

64. Baltenberger EP, Schmitt G, Thomas CJ (2014) Treatment of depressive symptoms in patients with cancer. Mental Health Clinician 4: 114-117.

65. Anderson IM, Nutt DJ, Deakin JF (2000) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology (Oxford, England) 14: 3-20.

66. Barbui C, Hotopf M (2001) Amitriptyline v. the rest: still the leading antidepressant after 40 years of randomised controlled trials. British Journal of Psychiatry 178: 129-144.

67. Mottram PG, Wilson K, Strobl JJ (2009) Antidepressants for depressed elderly. Cochrane Database of Systematic Reviews 25: CD003491.

68. Chochinov HM, Hack T, McClement S, Linda Kristjanson, Mike Harlos (2002) Dignity in the terminally ill: An empirical model. Soc Sci Med 54: 433-443.

69. Chochinov HM, Hack T, Hassard T, Linda J Kristjanson, Susan McClement, et al. (2002) Dignity in the terminally ill: A cross-sectional cohort study. Lancet 360: 2026-2030.

70. Chochinov HM (2002) Dignity-conserving care: A new model for palliative care. JAMA 287: 2253-2260.

71. Chochinov HM (2004) Dignity and the eye of the beholder. J Clin Oncol 22: 1336-1340.