Cognitive Deficits Associated With Cancer: A Model of Subjective and Objective Outcomes

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Abstract

Cancer and its treatment can affect many different aspects of quality of life. As a construct measured subjectively, quality of life shows an inconsistent relationship with objective outcome measures. That is, sometimes subjective and objective outcomes correspond with each other and sometimes they show little or no relationship. In this article, we propose a model for the relationship between subjective and objective outcomes using the example of cognitive function in people with cancer. The model and the research findings on which it is based help demonstrate that, in some circumstances, subjective measures of cognitive function correlate more strongly with psychosocial variables such as appraisal, coping, and emotions than with objective cognitive function. The model may provide a useful framework for research and clinical practice in quality of life for people with cancer.

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In oncology, treatment advances leading to improved survival have meant that quality of life issues have assumed greater significance in the past few decades. One such issue is cognition. Comparison of reviews over time shows the increasing interest in and evidence base for neuropsychological impacts of cancer and cancer treatments (for example, Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Cull, 1990; Meyers, 2000; Silberfarb, 1983). Although neuropsychological issues may seem most relevant when cancer directly involves the brain, through either primary or secondary brain tumours, there are a number of additional ways in which cognition can be altered in people with cancer.

In examining the literature on cognitive function in people with cancer, we were struck by the lack of integration between neuropsychological and quality of life accounts. More recent work has used a more integrated approach (Cull et al., 1996; Poppelreuter et al., 2004; Tannock, Ahles, Ganz, & Van Dam, 2004). Neuropsychology has developed valuable methods for quantifying cognitive function, focusing mostly on objective measurement, whereas the construct of “quality of life” focuses on subjective experience (Bowling, 1991). To facilitate clinical and theoretical applications, this article examines the literature on subjective and objective cognitive function in people with cancer and proposes a model. The review is not exhaustive, but is intended to provide guidance for further theoretical development. The proposed model also has the potential to stimulate further exploration of the relationship between subjective and objective outcomes in domains other than cognitive function.

First, theoretical and empirical bases of objective and subjective cognitive function are discussed. Next, research findings in people with cancer are examined. The model is then presented. The final section discusses clinical implications.

Objective and Subjective Cognitive Function and Emotions

Theoretical Background

The distinction between objective and subjective cognitive performance has been raised by a number of authors (for example, Cull et al., 1996; Tannock et al., 2004) and needs closer attention in determining appropriate practice regarding assessment and management of cognitive problems. Objective cognitive function is most accurately assessed by neuropsychological tests that meet psychometric criteria such as reliability and validity and are referenced to appropriate normative values. Deficits associated with cancer are sometimes global, such as delirium (Boyle, Abernathy, Baker, & Wall, 1998), but can often be more usefully described in terms of specific cognitive functions, such as attention, memory, or executive processes (Troy et al., 2000).

People's perceptions of their cognitive function have a different theoretical basis to objective indicators. Subjective perceptions are important in terms of the construct of "quality of life" which is considered to be multidimensional and subjective (Bowling, 1991). However, these perceptions sometimes show little or no relationship with objective measures of cognitive performance but instead correlate with emotional distress (Cull et al., 1996; van Dam et al., 1998). A dominant paradigm in the chronic illness field used to account for individual differences in subjective outcomes is the Lazarus and Folkman (1984) stress and coping model. According to stress and coping theory, outcomes that occur in response to a stressor are mediated by the individual's appraisal of the stressor and his or her coping resources and strategies. Reviews by Sabbioni (1991) and Temoshok (1987; 1991) have found significant associations of variables such as stress, appraisal, coping, and personality with physical and emotional outcomes in people with cancer. More research is required on the relationship between stress and coping predictors and subjective cognitive function, but a

number of studies have explored the connection with emotional distress, as summarised in the following section.

Empirical Findings

Several research groups have shown that people with health problems who reported subjective cognitive decrements were more likely to have emotional difficulties than objective deficits. Subjective cognitive impairment was more strongly related to depression and anxiety than to objective performance in people aged under and above 50 years who attended a memory clinic (Derouesne, Lacomblez, Thibault, & LePoncin, 1999), people who underwent surgery (Johnson et al., 2002; Moller et al., 1998), people with multiple sclerosis (Maor, Olmer, & Mozes, 2001), and people with chronic fatigue (Short, McCabe, & Tooley, 2002). Similarly, affect and personality were more predictive of memory and concentration complaints in haemodialysis patients than were neuropsychological or medical factors (Brickman, Yount, Blaney, Rothberg, & Kaplan De-Nour, 1996). For people with memory problems, patients' cognitive complaints correlated with depression but not with neuropsychological test performance and did not predict which patients developed dementia in the next two years (Tierney, Szalai, Snow, & Fisher, 1996). A study of 302 community-dwelling adults aged 75 years who did not have dementia found that subjective memory problems were not correlated with objective memory performance but showed small, significant correlations with depression and anxiety (Jungwirth et al., 2004).

Other studies have found subjective cognitive performance to be unrelated to emotional distress and associated with objective cognitive functioning. For people with acquired brain injury, a memory questionnaire and daily memory checklist correlated with neuropsychological tests of memory (Ownsworth & McFarland, 1999). Similarly, subjective cognitive deficits have been associated with the risk of developing a first psychotic episode in people at elevated risk of schizophrenia (Hambrecht, Lammertink, Klosterkotter, Matuschek,

& Pukrop, 2002), the risk of developing dementia in elderly adults with normal Modified Mini-Mental State Examination score at baseline after controlling for age, gender, and depressive symptoms (St John & Montgomery, 2002), memory, attention, and executive function scores in people with multiple sclerosis (Matotek, Saling, Gates, & Sedal, 2001; Randolph, Arnett, & Higginson, 2001), neuropsychological performance in people with subjective memory impairment (Clarnette, Almeida, Forstl, Paton, & Martins, 2001), and the extent of white matter lesions measured with magnetic resonance imaging in 1,049 older adults who did not have dementia (de Groot et al., 2001).

Inconsistent findings regarding the associations between subjective cognitive functioning and both emotional distress and objective performance may be due to variations in operational definitions and measurement of subjective impairment. Studies that have found closer correspondence between subjective and objective cognitive measures appear to have more often used specific behavioural checklists (for example, Ownsworth & McFarland, 1999) and included control groups (for example, Clarnette et al., 2001; Matotek et al., 2001). Reports of changes in cognitive function may be more closely linked to objective function than participants' estimates of absolute function (de Groot et al., 2001; Hambrecht et al., 2002). Stronger associations between subjective and objective performance have been reported in people with higher levels of either education (Randolph et al., 2001) or objective performance (de Groot et al., 2001).

Emotions and Objective Performance

A further consideration in understanding the role of emotional distress is the link between it and objective performance (Cull, 1990). Reviews have found that approximately 25-45% of people with cancer show significant psychiatric difficulties, such as depression and anxiety, associated with diagnosis and treatment (Harrison & Maguire, 1994; Hughes, 1987). In both younger and older adults without cancer, major depression has been associated with

deficits in attention, memory, language and perception (Christensen, Griffiths, MacKinnon, & Jacomb, 1997; Lamberty & Bieliauskas, 1993). Sub-clinical depression does not appear to significantly affect cognitive function (Lamberty & Bieliauskas, 1993). A diagnostic category of “pseudodementia” is sometimes used for people who show cognitive impairment presumed to be secondary to depression, which is remediated if depression is successfully treated (Antikainen et al., 2001; Lezak, 1995). These impairments may affect only some individuals with depression, and are seen as “an attentional-motivational deficit” (Lezak, 1995).

Neurological and psychosocial studies have supported an influence of emotions on cognitive processes (Ciompi, 1991). For example, positron emission tomography scans of 10 young men undertaking verbal information-processing tasks showed differential cognitive processing with mood. Depressed mood, but not neutral or elated moods, attenuated task-related activation in anterior cingulate cortex (a brain area involved in executive and emotional functions; Baker, Frith, & Dolan, 1997). Clinically depressed people (Winter & Kuiper, 1997) or healthy individuals experiencing experimentally-induced depressive states (Varner & Ellis, 1998) show increased recall of negative emotion words. In contrast, nondepressed people show greater recall for positive adjectives, and mildly depressed recall an equal balance of both (Winter & Kuiper, 1997). Similarly, anxious people display greater attention to and recall for fear-relevant stimuli (Winter & Kuiper, 1997). Thus, emotional states can affect cognitive processes such as attention and memory.

Neurological dysfunction that disrupts cognition can also cause emotional distress, either directly or as a secondary reaction to loss of abilities (Hughes, 1987; Meyers, 2000; Reitan & Wolfson, 1997). For example, when chemotherapy was supplemented with interleukin treatment, both negative mood and cognitive impairment increased in patients, compared with chemotherapy alone (Walker et al., 1997). Affective symptoms in people with cancer may indicate underlying neurological deficits (Oxman & Silberfarb, 1987). In one

series of 100 consecutive psychiatric referrals from an oncology service, 40 people showed evidence of an organic brain syndrome and, importantly, 26 of these had not been recognised by the referring physician (Levine, Silberfarb, & Lipowski, 1978).

In summary, people who experience significant emotional disruption associated with cancer may be at risk of cognitive dysfunction secondary to emotional disturbance. If this occurred, the expected pattern of performance would be intact temporal orientation and relatively intact performance on recognition tasks, even if immediate recall were impaired (Lezak, 1995). Emotional disruption and cognitive impairment can also have a common cause, being due to underlying neurological dysfunction.

Based on the reports described above, subjective cognitive assessment cannot be assumed to be a good indicator of objective cognitive function, unless the instrument's validity for this purpose has been established. Subjective reports appear to cover a spectrum from those sharing substantial variance with emotional distress but none with objective performance, to those with strong correspondence with objective performance and no correspondence with affect. We therefore consider objective and subjective cognitive changes separately in reviewing a sample of studies on contributing factors during the following sections. More detailed reviews on this topic include those by Meyers (2000) and Reeb and Regan (1998). A meta-analysis by Anderson-Hanley and colleagues provides a quantitative overview (Anderson-Hanley et al., 2003).

Objective Cognitive Function

Tumour Effects

The risk of impairment differs according to the site of malignancy. Presently available data limit comparisons of the nature and prevalence of cognitive impairment between specific types of cancer because cognitive effects have been defined and measured differently by separate researchers (Armstrong, Gyato, Awadalla, Lustig, & Tochner, 2004; Weitzner &

Meyers, 1997). Patient groups that have recently been considered as susceptible to cognitive dysfunction include those with primary or secondary brain tumours (Weitzner & Meyers, 1997), small-cell lung cancer (Klein et al., 2001), and terminal malignancies from a variety of primary sites (Bruera et al., 1992; Pereira, Hanson, & Bruera, 1997).

Localised or metastatic tumours in brain are thought to frequently disrupt mental functions, especially problem-solving skills and coping with novel situations (Meyers, 2000; Weitzner & Meyers, 1997). In summarising literature with wide variation in definitions and methods of assessing impairment, previous reviewers have concluded that cognitive impairments affect a high number of people with primary or secondary brain tumours, especially if subtle impairments are included (Benesch et al., 2001; Weitzner & Meyers, 1997). Rates of neuropsychological impairment as high as 100% have been reported, in 68 people who had neurosurgery for recently diagnosed glioma compared with healthy controls (Klein et al., 2001). However, this figure is likely to overestimate changes that are clinically significant. Metastatic tumours to brain are relatively common, occurring in 20-40% of patients with non-neurological solid primary malignancies (Meyers, 2000).

Tumours can also have indirect, nonlocalised effects on brain function. Of eight people with multiple myeloma admitted to a general hospital, four exhibited delirium (Silberfarb & Bates, 1983). Many people with small-cell lung cancer exhibit subclinical impairments in memory and planning before treatment, in the absence of brain metastases (Meyers, 2000). In comparisons with people without cancer, a 52% rate of neuropsychological impairment was found among 50 people with small-cell lung cancer (Klein et al., 2001). A slowly progressive neurological syndrome has been described in treated patients with small cell lung cancer but without central nervous system metastases, 26-50 months after cranial irradiation and systemic chemotherapy (So, O'Neill, Frytak, Eagan, & al, 1987). The 6 patients described by So et al. showed apathy, abulia, memory loss, gait

ataxia, and corticospinal tract signs. Certain leukaemia patients are potentially at risk of cognitive impairment because of elevated circulating levels of cytokines, which have been associated with cognitive and mood dysfunction (Licinio, Kling, & Hauser, 1998; Walker et al., 1997).

Advanced disease appears to significantly increase cognitive vulnerability. Systemic effects of tumours that can disrupt cognitive function in advanced cancers include hypercalcaemia caused by bone metastases (Boyle et al., 1998), metabolic disturbances and infections (Meyers, 2000) as well as multiple system failure terminally (Pereira et al., 1997). Both prospective and retrospective studies have shown that as many as 68-83% of people receiving palliative care for terminal cancer scored in the impaired range on the Mini-Mental Status Examination at some time before death (Bruera et al., 1992; Pereira et al., 1997). Sepsis and brain metastases were the most frequently identified causes of impairment in these patients, after medications which were the most frequent cause (Bruera et al., 1992; Pereira et al., 1997). Further research with specific groups of people with cancer would be beneficial, especially if more studies included non-cancer comparison groups.

Treatment Effects

The potential for cognitive deterioration can also increase due to treatment. Cancer treatments that have been associated with cognitive impairment include chemotherapy, cranial irradiation, cytokines, hormonal ablation, palliative medications, and anticholinergic drugs.

Chemotherapy. Many different chemotherapy agents or combinations of agents have been associated with adverse cognitive changes (Boyle et al., 1998; Hughes, 1987). Neurotoxic agents most frequently affect visuoperceptual, psychomotor constructional skills, reaction time, verbal conceptualisation, short-term memory, attention, and executive processes, possibly through selective actions on the frontal lobes, hippocampus and amygdala (Troy et al., 2000). In other words, diffuse effects are seen on tests requiring sustained

attention and rapid information processing (Meyers, 2000). For example, of 28 women aged 28-54 who had undergone chemotherapy for breast cancer within the last 12 months but not within 2 weeks of testing, 75% scored in the range of moderate cognitive impairment compared with age, gender and education norms on a comprehensive neuropsychological battery (Wieneke & Dienst, 1995). The group performed significantly lower than norms in five of seven cognitive areas, with only verbal fluency and abstract reasoning remaining intact.

Neurotoxic effects of chemotherapy are usually reversible but sometimes persist after treatment ends (Cull, 1990). Of women with breast cancer who were randomly assigned to high- or standard-dose chemotherapy, cognitive impairment two years after treatment was found in 32% of women in the high-dose group, compared with 17% of women assigned to standard-dose, and 9% of women with Stage I breast cancer who were not treated with chemotherapy (van Dam et al., 1998). Significant neurophysiological differences were also detected in a subset of the women tested with quantitative electroencephalograms at two years post-treatment: asymmetry of the alpha rhythm of at least 5 Hz was found in 7/17 high dose patients, 2/16 standard dose patients, but 0/14 comparison group patients (Schagen, Hamburger, Muller, Boogerd, & van Dam, 2001).

A strength of the study of van Dam and colleagues was its use of random assignment to treatment. The study demonstrated that the risk of cognitive impairment increased with higher chemotherapy doses. Fortunately, the cognitive deficits appeared to have remediated by 4-year follow up, although there were some indications of differential attrition of participants with lower baseline cognitive scores because of increased rates of disease progression (Schagen et al., 2002). Another research group found that, of 128 patients who were disease-free at least 5 years after diagnosis with breast cancer or lymphoma, those treated with systemic chemotherapy scored significantly lower on a battery of

neuropsychological tests than those treated with local therapy (Ahles et al., 2002). Deficits were found after controlling for age and education and were most pronounced for verbal memory and psychomotor functioning (Ahles et al., 2002). These chemotherapy treatment studies have provided stronger evidence of impairment than studies using mental status examinations, because they used well-developed measures of specific functions and compared patients' performance with either normative data or other patient groups. A recent review of psychometrically controlled chemotherapy studies in women with breast cancer found that studies reported cognitive deficits in 16-50% of participants (Tannock et al., 2004).

Radiotherapy. Radiotherapy has been associated with cognitive impairment in some individuals, including both children (Cousens, Waters, Said, & Stevens, 1988; Eiser, 1998) and adults (Armstrong et al., 2004; Olson, Riedel, & DeAngelis, 2000). Cranial irradiation produces the greatest cognitive risk (Eiser, 1998), due to damage of subcortical white matter (Armstrong et al., 2004; Meyers, 2000). A number of studies have reported increased cognitive effects from cranial irradiation in children younger than 5 at the time of treatment (Cousens et al., 1988; Kaleita, 2002; Winqvist, Vainionpaa, Kokkonen, & Lanning, 2001), although others have found no age effect (Iuvone et al., 2002). Because of such findings, cranial irradiation is now avoided for infants younger than 2 years (Eiser, 1998). A recent review has outlined a number of aspects of cognitive impairment associated with cranial radiotherapy, including evidence for a dose-response relationship and differences between early, largely reversible deficits found within several months of radiotherapy and persisting deficits, which are more often associated with late effects that develop 12 months or more after treatment (Armstrong et al., 2004).

In 20 adults treated with cranial radiotherapy for low-grade brain tumours, verbal-semantic recall was impaired, but other attentional and memory processes were not affected (Armstrong, Stern, & Corn, 2001). Of 62 people with low grade oligodendrogliomas or

mixed gliomas who received radiotherapy, radiotherapy-associated cognitive changes were found in 13 people (Olson et al., 2000). In contrast, a study of 13 adults with brain tumours found cognitive deficits before radiotherapy in attention, memory and visuospatial construction compared with healthy controls, but these deficits did not worsen when participants were retested 2 weeks and 3 months after completing radiotherapy (Lilja, Portin, Hamalainen, & Salminen, 2001).

Cytokines. Cytokine treatment with interferon has been associated with impaired performance on attentional tasks, such as Digit Symbol and Trailmaking B (Capuron, Ravaud, & Dantzer, 2001; Licinio et al., 1998). Deficits were significantly worse in people who received cytokines combined with chemotherapy, compared with chemotherapy alone, and impairments were reversed with cessation of cytokine treatment (Walker et al., 1997). The early onset of cytokine cognitive effects was shown in a study which found that people treated with interleukin-2 showed a decline in performance in spatial working memory and planning that was apparent at both 5 days and 1 month of treatment compared with pre-treatment (Capuron et al., 2001). In the same study, people treated with interferon alpha showed no deficits in those tasks but instead showed increased reaction times (Capuron et al., 2001). These findings emphasise the potential for exogenously produced and delivered cytokines to impair cognition, and draw attention to the need to measure cognitive effects of endogenous (internally produced) cytokines as mentioned earlier.

Hormonal Ablation. Several reviews have noted associations between hormonal ablation treatments, such as those used for breast or prostate cancer, and cognitive impairment (Olin, 2001; Tannock et al., 2004; Thompson, Shanafelt, & Loprinzi, 2003). In a randomised 12-month clinical study completed by 62 men with prostate cancer, men assigned to hormonal ablation with leuprorelin, goserelin, or cyproterone acetate showed cognitive deficits in memory, attention, and executive function compared with their baseline performance and the

performance of no-treatment controls (Green et al., 2002; Green et al., 2004). A study of 19 men treated with 9 months of intermittent androgen suppression with leuprolide and flutamide, compared with community controls, found that spatial rotation performance declined during androgen blockade but most cognitive functions were unimpaired (Cherrier, Rose, & Higano, 2003). Salminen and colleagues also found that 25 men treated for 12 months with androgen deprivation for prostate cancer showed practice effects and did not decline in cognitive performance (Salminen et al., 2003). A recent review of cognitive studies in women with cancer suggested that one of the routes of impairment associated with chemotherapy may be endocrine effects resulting in accelerated loss of sex steroids (Olin, 2001).

Surgery. Surgical procedures, especially in older adults, have been associated with adverse cognitive effects in both acute (Milisen, Abraham, & Broos, 1998) and longer-term phases (Goldstein, Fogel, & Young, 1996). While cognitive effects of cardiac surgery have been known for some time (Emskoetter & Lachenmayer, 1990), adverse cognitive effects of non-cardiac surgery have been also been demonstrated in both small-sample studies using mental status examination (Milisen et al., 1998) and large international studies using comprehensive neuropsychological testing and control groups (Johnson et al., 2002; Moller et al., 1998). Of 1218 adults aged 60 or more who underwent non-cardiac surgery, 26% were impaired on a neuropsychological battery 1 week after surgery and 10% remained impaired 3 months later (Moller et al., 1998). A related study in adults aged 40-60 who had non-cardiac surgery found postoperative cognitive impairment in 19% at 1 week and 6% at 3 months (Johnson et al., 2002). Surgical treatments for cancer would be predicted to lead to acute cognitive deficits for some individuals and chronic impairments for a smaller proportion of patients. In support of this prediction, impaired attentional performance post-surgery, compared with pre-surgery, has been found in women treated for breast cancer (Cimprich,

1998). However, the study did not establish whether deficits persisted. Many other surgical treatments for cancer have yet to be assessed for cognitive effects.

Additional Treatments. Several other treatments have shown some evidence of cognitive effects. In a group of 40 adult patients assessed at least 2 years after bone marrow transplantation, 60% showed mild to moderate cognitive impairment on neuropsychological tests compared with community norms (Harder et al., 2002). Palliative medications that have been associated with impairment include analgesics, such as opioids (Pereira et al., 1997), corticosteroids, such as prednisone (Wolkowitz, Reus, Canick, Levin, & Lupien, 1997), psychotropic medications (Meyers, 2000), and antiemetics (Meyers, 2000). The potential for cognitive impairment associated with anticholinergic medications, especially in elderly people, is also increasingly recognised (Mintzer & Burns, 2000; Tune, Carr, Hoag, & Cooper, 1992).

Subjective Cognitive Function

Concerns about adverse subjective cognitive effects associated with cancer or its treatment have become increasingly common among cancer support groups, leading to use of terms such as “chemo-brain” (Tannock et al., 2004). Within oncology, comparatively few researchers have measured both objective and subjective cognitive function. Similar to the literature in people with other health conditions discussed above, some studies have found emotion-linked subjective performance and others have found correlated subjective and objective deficits.

Cull and colleagues found that, of 91 adults treated for lymphoma at least six months previously (62 with chemotherapy, 27 with no chemotherapy, and 2 with treatment not reported), 52% reported memory problems and 30% difficulty concentrating (Cull et al., 1996). However, self-reported deficits did not correlate with objective performance and were instead associated with higher anxiety, depression, and fatigue. This suggested to the

researchers that perceived decrements in cognition were more closely related to emotional and physical status than objective cognitive functioning (Cull et al., 1996). Similarly, in women treated with standard- or high-dose chemotherapy for breast cancer, two measures of subjective cognition correlated with each other and with anxiety and depression, but showed no relationship with objective cognitive function (van Dam et al., 1998). A study of 102 people with cancer of areas other than brain, before and after chemotherapy, found that a subjective cognitive measure had no correlation with Mini-Mental Status Examination score but correlated significantly with anxiety and depression (Iconomou, Mega, Koutras, Iconomou, & Kalofonos, 2004). In 61 people with cancer aged 25-87, the subjective item 11 on the Zung Self-Rating Depression Scale “My mind is as clear as it used to be” correlated with depression and showed poor sensitivity and specificity in identifying cognitive dysfunction as measured by a Trail-Making task, a Stroop task, and the Dementia Rating Scale (Kibiger, Kirsh, Wall, & Passik, 2003).

One study specifically designed to examine the relationship between subjective and objective cognition in people with cancer found that 24% of the 119 participants showed clinically impaired neuropsychological performance. However, there were no significant correlations between neuropsychological test performance and subjective reports of everyday cognitive performance (Poppelreuter et al., 2004). These subjective reports instead correlated with affective measures, more strongly with depression than anxiety (Poppelreuter et al., 2004). In contrast, for people who remained progression-free for at least 2 years after bone marrow transplantation, subjective cognitive complaints did correlate significantly with moderate to severe cognitive deficits measured by neuropsychological testing (Harder et al., 2002).

A Model of Cognitive Function in People With Cancer

Based on the above literature, Figure 1 proposes a model of factors contributing to cognitive impairment in people with cancer. Objective and subjective impairment are presented as separate outcomes. The article has discussed two parts of the model in detail: the links between objective and subjective cognitive function and emotion, and tumour and treatment effects on cognitive function. Findings that psychosocial factors can influence emotional distress and correlate with physical health have been incorporated as a pathway in the model.

Insert Figure 1 about here

Three factors contributing to objective impairment are proposed: physical health, medical treatments, and emotions. Within predictors listed under physical health, tumour effects have received the most focus in this article. Previous reviews have discussed other physical health cognitive predictors, including age (for children, see Challinor, Miaskowski, Moore, Slaughter, & Franck, 2000; Chen et al., 1998; for cognitive aging see Luszcz & Bryan, 1999; Riedel & Jolles, 1996) and general medical conditions (Siegler & Vitaliano, 1998; Zelinski, Crimmins, Reynolds, & Seeman, 1998). Researchers specifically addressing chemotherapy have proposed a model which shares some similarities with the current model (Tannock et al., 2004); however, the model presented in this paper was developed independently.

Clinical Implications

Assessment

Identification of and treatment for cognitive deficits is important, since cognition is a key variable determining whether people can live independently or with minimal assistance (Wang, van Belle, Kukull, & Larson, 2002). Cognitive assessment can provide information needed to plan practical issues such as transport, work, and support needs. Assessment may

also assist staff to tailor communication, such as reducing information processing demands for patients who have difficulty sustaining attention. Cognitive and emotional function should be assessed at presentation and on an ongoing basis.

Screening measures for global dysfunction were reviewed by Boyle and colleagues (Boyle et al., 1998). The review identified several relatively brief measures that can detect generalised dysfunction, have demonstrated sensitivity to cognitive changes in people with cancer, and can be administered frequently (Breitbart et al., 1997; Folstein, Folstein, & McHough, 1975; Neelon, Champagne, Carlson, & Funk, 1996; Williams, 1991). For inpatients with advanced malignancy, mental status examination as often as three times per week has identified cognitive dysfunction in some patients that had not previously been recognised by medical or nursing staff (Bruera et al., 1992).

When more detailed assessment is required, referral to a neuropsychologist or clinical psychologist with neuropsychological expertise allows assessment with standard tests that provide more specific information about the nature and severity of cognitive dysfunction and are able to detect more subtle forms of impairment. Major cognitive domains to assess include attention, memory, language, visuomotor, and executive functions. For surgical patients, a useful research battery for detecting postoperative cognitive function included visual verbal learning (based on Rey's Auditory Verbal Learning Test; Lezak, 1995), concept shifting (based on Trailmaking; Lezak, 1995), the Stroop colour word interference test (Sprenen & Strauss, 1991), letter-digit coding (based on Digit Symbol; The Psychological Corporation, 1997), and a paper and pencil memory scanning test (Moller et al., 1998). The same or similar tasks have shown sensitivity to cognitive effects of cancer treatments (van Dam et al., 1998; Walker et al., 1997; Wieneke & Dienst, 1995).

If subjective cognitive function is of concern, behavioural checklists that have shown associations with objective deficits in people without cancer include the Daily Memory

Checklist (Ownsworth & McFarland, 1999), Cognitive Failures Questionnaire (Broadbent, Cooper, Fitzgerald, & Parkes, 1982), Subjective Memory Questionnaire (Bennett-Levy & Powell, 1980), and an inventory of everyday memory experiences (Herrmann & Neisser, 1978). Measures such as the two-item Cognitive Function subscale (Fayers, Aaronson, Bjordal, & Sullivan, 1997) and interview for cognitive problems in daily life (van Dam et al., 1998) have been associated more closely with emotional distress than objective cognitive function in reports to date.

Interventions

Interventions suggested by this model include incorporating individual patient susceptibility when planning treatment, educating patients and families about current and anticipated cognitive function, identifying factors contributing to an individual's difficulties, and remediating these factors when possible. Staff should be informed so that they can tell patients that procedures such as chemotherapy and cranial radiotherapy are associated with cognitive dysfunction for some individuals and that, in many situations, there is likely to be improvement over time if treatments disrupt cognition (Moller et al., 1998; Walker et al., 1997). In people with elevated risk of cognitive dysfunction, all potentially problematic medications and procedures should be reviewed before embarking on definitive cancer treatment which may adversely affect cognition.

Treating cognitive dysfunction associated with cancer has previously been described for both terminal (Boyle et al., 1998; Bruera et al., 1992) and earlier stage (Butler & Copeland, 2002; Meyers, 2000) cancer. One protocol for people with terminal cancer initiated investigation whenever MMSE was less than 24 or decreased more than 30% from previous function (Bruera et al., 1992). If these criteria were met, medical and laboratory evaluations were undertaken, medications were reviewed and, if possible, all drugs that could contribute to cognitive dysfunction were discontinued or reduced in dose. Additionally, if

indicated by the medical examination, computerised tomography or pulse oximetry was performed (Bruera et al., 1992). We recommend that emotional distress should also be evaluated and treated. Also, alternative criteria for cognitive dysfunction should be considered, given the limitations of the MMSE.

Pharmacological agents may assist in preventing (Troy et al., 2000) or remediating (Weitzner & Meyers, 1997) cognitive impairment associated with cancer treatment. However, before adding medications, it is prudent to review those currently being prescribed so that preparations with adverse cognitive properties might be removed or replaced with alternatives. Alberts and Noel (1995) reviewed the potential for agents such as nerve growth factor and amifostine to prevent neurotoxicity associated with cisplatin. Methylphenidate has been reported to have benefits for alleviating cognitive dysfunction in people with cancer (Rozans, Dreisbach, Lertora, & Kahn, 2002; Weitzner & Meyers, 1997), including in a randomised placebo-controlled trial which found a specific benefit for sustained attention (Thompson et al., 2001). Corticosteroid use was also reported to have possible cognitive benefits for people with gliomas (Klein et al., 2001) or treatment-associated leukoencephalopathy (Noble & Dietrich, 2002) although this class of drugs has also been implicated in adverse cognitive effects (Wolkowitz et al., 1997). Neural stem cells have been suggested as a possible future avenue for treating both brain tumours and treatment-associated cognitive dysfunction (Noble & Dietrich, 2002). However, any effort to modify adverse impacts needs to be considered in the context of the overall patient and cancer program.

Cognitive rehabilitation treatment may also assist, especially for persisting impairment (Meyers, 2000; Wilson, 1997). Ideally, cognitive rehabilitation addresses cognitive problems in the context of social, emotional, and functional difficulties (Wilson, 1997). Assessment of impairments in these domains and the impact of impairments on daily life is followed by individual or group therapy designed to overcome the effects of impairments (Ownsworth &

McFarland, 1999; Weitzner & Meyers, 1997). Multidisciplinary rehabilitation teams, including health professionals such as psychologists, speech pathologists and occupational therapists, are recommended (Weitzner & Meyers, 1997; Wilson, 1997). Cognitive rehabilitation programs have begun to be reported for people with cancer, including children (Butler & Copeland, 2002) and older adults (McDougall Jr, 2001).

Conclusion

The research studies discussed in this paper support the proposition that cancer and its treatment is linked in a significant minority of patients with cognitive dysfunction serious enough to warrant investigation and treatment. Subjective perceptions of cognitive impairment are important to quality of life and sometimes show significant relationships with objective measures. However, this is not true of all subjective measurement; other measures are associated with emotional distress more strongly than with objective function. Further research needs to inform clinicians so that they might consider multiple causal pathways associated with cognitive dysfunction, including precancer function, comorbid conditions, tumour effects, depression, anxiety, and current medical treatments, in order to minimise adverse effects from both tumour and treatment in at-risk patients. The subjective and objective distinction also needs further attention for other, non-cognitive outcomes associated with quality of life.

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Figure Captions

Figure 1.

A proposed model of factors contributing to objective and subjective cognitive impairment in people with cancer. The model follows conventions of path diagrams (Loehlin, 1992): straight arrows indicate putative causal relationships, curved arrows indicate putative correlations between source variables, and residual arrows on the dependent variables (emotional health, objective impairment, and subjective impairment) are used to indicate possible additional sources of variance in dependent variables apart from the source variables directly represented in the diagram.