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Quality of life in patients with brain tumor: what's relevant in our quest for therapeutic efficacy

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Quality-of-life assessments in neurooncology are becoming more relevant with the proliferation of intensive research into brain tumors and their therapy. In this review, the authors examined several aspects and problems associated with the past, present, and future applications of quality-of-life assessments in neurooncology.

The inadequacy of the almost exclusive use of physical functioning assessments, image-documented tumor response to therapy, and patient survival time as endpoints when evaluating therapeutic regimens is becoming increasingly apparent. In therapies in which outcome using traditional endpoints are only marginally different, specific (neurological) toxicity and social and psychological outcomes must be evaluated as well to determine valid treatment options. Also becoming widely accepted is the consideration of patient values of specific health states in justifying treatment resources. There is ongoing research in brain tumor patients to address these issues.

Key Words * quality of life * brain tumor patient * utility * multidimensional assessment

The increasing intensity of brain tumor research, especially in the study of tumor genetics, invasion, and impairment of normal functioning brain, as well as novel therapies that sometimes involve combining potent modalities, have renewed interest in tumor and treatment effects on quality of life (QOL).

The more traditional outcome measures of change in tumor size on imaging, patient survival time, and physical toxicity effects have not adequately evaluated the multiplicity of brain functions involved or the residual capabilities of surviving patients, especially in the context of their social functioning. Aside from methodological considerations, it is becoming more clear that cancer patients themselves are concerned with maintaining QOL as well as reducing the threat to their survival.[31] Most important, there is increasing evidence that mind does indeed matter in the fight against cancer[55] and that preserving psychosocial functioning, and instituting therapeutic measures that improve it, positively influence survival.[15-17,56]

REVIEW OF QUALITY OF LIFE APPLICATIONS

Validity and Quality of Life Assessment in Neurooncology

In neurooncology assessments, physical functioning measures such as the Karnofsky Performance Scale (KPS)[29] or World Health Organization clinical performance status have traditionally been used longitudinally to evaluate the QOL of patients.[5,10,32,34,39,45,59,65] This approach is usually combined with the assessment of conventional measures such as survival duration, time to relapse, and imaging-documented changes in tumor size.[12,13,18,28,35] The toxicity of therapy has also been assessed, for the most part, in categorical terms such as "major" or "minor" morbidity and mortality.[8,9,11] Although a number of investigators have attempted to evaluate cognitive and psychosocial function,[1,23,24,60,66,69,70] relatively few reports of these evaluations appear in current literature. In the second major use of QOL measures--selection of patients to be included in a clinical trial[61]--physical outcome measures have been used predominantly[6,28,54,59,65] (Table 1).

TABLE 1 APPLICATIONS OF QOL ASSESSMENTS IN NEUROONCOLOGY	
Primary Uses of QOL	Summary of Assessments
1) to evaluate therapy in prospective trials	generally reported in association w/ survival times
2) to select patients for prospective trial	most reports used physical outcome measures
3) to assess treatment-related toxicity	specific instruments used to evaluate toxicity; may help determine therapeutic guidelines/standards
4) to assess multidimensional domains in QOL	may reveal psychosocial/treatment-related toxicity; intervention could be used to improve QOL or survival

Some investigators have criticized the undue emphasis placed on "hard" data endpoints (such as survival) in evaluating patients with brain tumor, pointing out that although these outcomes can be accurately and reliably measured, they may be of questionable relevance to patients. These investigators have advocated assessing self-reported QOL determinations that, although subjective, reflect real patient concerns.[49,52] Such advocacy does not diminish the importance of survival to these patients.[15-17,31,55,57] It reflects, however, their documented concerns with disease and treatment-related limitations, particularly with permanent disabilities.[31] Ultimately, however, there is little debate about the need to assess QOL thoroughly in terms relevant to patients, because the objective in our pursuit of efficacious therapeutic regimens is improving both the quantity and the quality of patient survival. The questions that remain are how to define patient concerns and how to develop methods for assessing them in a valid manner.

Utility-Based QOL Assessment

Readily integrated with survival analysis, one approach to QOL assessment is utility-based evaluation. Utility measures yield a single value between zero and one, indicating the strength of the patient's preference for a specific health-related outcome, which is most often their own current state of health. The utility of an outcome or health state therefore reflects not only health status but the patient's valuation of that status. As such, utility measures offer a unique set of advantages in QOL measurement. First because patient preferences are assessed, utility measures evaluate the meaning of disability to the individual, assessing how a specific disability affects the patient's structure of preferences. This utility measurement thereby provides information about how patients assess themselves in specific QOL domains as well as how important particular domains are to their perception of overall status. This aspect

of utility measurement becomes clearer if we consider two patients with similar levels of memory dysfunction: although each patient has an identical degree of functional disability, each may place different values on the same level of dysfunction,[2] especially if one patient tolerates the dysfunction well and the other patient finds it very disabling. Such varying values are captured in the different utilities each patient assigns to the same dysfunctional level. Thus, utility measures are responsive to the unique way each patient experiences dysfunction.

Furthermore, utility measures combine all aspects of health status within a single measure, and thus, in treatment evaluations, benefit and toxicity are captured in one measure. Additionally, utility measures provide a generic unit of QOL that permits comparisons of different health interventions in divergent patient groups. This is valuable in economic evaluations because a common unit of health measurement can compare different interventions in different populations and lead to an understanding of the comparative economic efficiency of competing health programs.[25,62] Finally, the utility-based approach is rooted in a theory that has dominated decision-making under conditions of uncertainty for four decades.[42] The reliability and validity of this approach have been demonstrated in numerous patient groups and illnesses.[21,22,30,63,64]

An excellent example of this approach is provided by the Radiation Therapy Oncology Group. In a hyperfractionated radiation dose escalation study in patients with malignant glioma who were also treated with carmustine, the best quality-adjusted survival time was observed in the group receiving 72.0 Gy.[41,53] This was assessed by medical professionals who assigned utility values for different clinical states and who took into account 15 neurological symptoms and signs of morbidity.[41,53] Although the medical professionals provided their values as a proxy for patient self-report, one can see how preference-based measurement serves to combine different valuations into a readily applicable score. On the basis of these results, the 72-Gy arm was selected for the phase III study.

Multidimensional "Profile" QOL Measurement

Multidimensional assessment entails discerning which QOL domains are significant for the greatest number of patients and then devising subscales to evaluate them adequately. Advocates point to the World Health Organization's definition of health ("a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity") as supportive of multidimensional measurement.[71] The question with multidimensional measures is how to ascertain whether the particular content of a scale is both valid and sufficiently comprehensive to assess accurately specific patient groups. Answering this question requires a content validation process (for example, through focus groups and/or semistructured interviews), eliciting systematic self-report from patients who represent the target patient group as a whole, and from clinicians, who represent an expert professional perspective.[48,58,70] With such approaches, it is possible to evaluate empirically, for instance, whether functional outcome as a proxy for global QOL in patients with brain tumor is adequate or lacking in some dimensions that should be optimally assessed in a comprehensive assessment.

The inevitable debate in multidimensional QOL measurement is whether generic instruments are sufficiently comprehensive and responsive to assess adequately different patient groups or whether disease-specific instruments must be developed for valid assessment. A combined strategy has worked effectively, in which a well-validated generic instrument is combined with a disease-specific inventory of supplementary measures in many disease groups.[48] Several investigators have used multidimensional instruments to assess the QOL in patients with malignant brain tumors[36,44,69,70] with core generic

instruments such as the European Organization for Research and Treatment of Cancer QLQ-C,[30,36,44,58] the Functional Assessment of Cancer Therapy scale,[70] or the Medical Outcomes Study Short-Form Health Survey measures (20- and 36-item forms)[40] supplemented by specific measures for brain tumor patients. In some of these instruments, one important aspect of QOL assessment is the evaluation of the importance respondents attach to each of the domains assessed; in other words, a utility-type evaluation.[69,70] These investigations provide some indication that this combined instrumentation is more sensitive in assessing QOL than the KPS, especially in patients who function independently (KPS score > 70). In the quest for more responsive and comprehensive QOL measurement, one, of course, confronts the dilemma of obtaining reliable and accurate self-reports from patients who are cognitively impaired because of their tumors and/or related treatments, and additional work is needed to address this challenge.[7,70]

The significance of multidimensional assessment of QOL in patients with brain tumor has been suggested by several intriguing findings in patients with other cancers, including breast and lung cancers and malignant melanoma.[15-17] Multidimensional studies have proven useful in the past when comparing different treatment policies, especially when the difference in survival in patients treated according to these policies has been marginal.[47] There is additional evidence that some aspects of multidimensional QOL are useful as prognostic indicators of survival and may actually outperform conventional predictors of survival such as performance status and tumor response.[15,16,27,67] Subjective variables such as "psychosocial well-being" and "general symptoms" were found to be independent predictors of survival in one study,[27] and in another study the "health" dimension of the Spitzer Quality of Life index[57] and the "physical well-being" and "appetite" dimensions of linear analog scores were found to independently predict survival.[16]

One reasonable interpretation of these findings is that psychosocial interventions affecting changes in these dimensions could theoretically influence survival in cancer patients; for example patients with metastatic breast cancer, who were randomly assigned to the psychosocial intervention arm, survived significantly longer than controls who did not receive weekly supportive group therapy.[56]

The mechanism of action or link between emotional processes and cancer course may be psychoneuroendocrinological in nature, specifically involving stress hormones such as prolactin or cortisol secretion; or it may be psychoneuroimmunological, that is, through regulation of the activity of immune cells such as natural killer cells.[55]

Another potentially important function of multidimensional assessment in patients is its capacity for identifying psychosocial dysfunctions that would not be otherwise detected. Neurological examinations and physical outcome assessment only address the physical manifestations of brain dysfunction and are not usually helpful in assessing cognitive-emotional functioning. With better screening of cognitive-emotional difficulties, psychosocial interventions could be applied to improve QOL and perhaps even extend survival in patients with these difficulties[38,67] (Table 1).

Studies showing the efficacy of psychosocial intervention on survival in cancer patients have been criticized: these patients may represent a self-selected group who are motivated to survive and may, thus, be inclined to comply more rigorously with medical treatment or have an improved appetite and/or diet because they may be less depressed.[56] Analysis of multidimensional QOL assessments in randomized phase III trials will help to answer this question. The recently completed University of Toronto Randomized Study of Brachytherapy for malignant glioma[4] included QOL assessments with a

multidimensional instrument developed at that institution.[7] The results of this study will be reported shortly. The feasibility of performing QOL and neuropsychological evaluation within a large multicenter trial has been tested in a companion study to Radiation Therapy Oncology Group.[14] The authors of this study found the Activity of Daily Living Scale[68] and the Mini-Mental State Exam,[20] which are used for QOL and neuropsychological evaluation, to be cost effective and provided additional information not produced by the results of the KPS.

Multidimensional QOL assessment, with specific emphasis on cognitive function measures, has been used to identify the devastating effects of combined craniospinal radio- and chemotherapy in survivors of medulloblastoma who were treated prior to 4 years of age.[34] As a result of these findings there is now increasing use of primary postoperative chemotherapy and deferred radiation therapy in children with medulloblastoma.[51] Multidimensional QOL considerations have also prompted deferred radiation therapy in the management of cerebral low-grade glioma.[3,33,43,46] Because we lack evidence that early aggressive treatment influences survival, a valid treatment option is to monitor patients with serial imaging and clinical assessment until signs of malignant evolution become manifest, at which time the patient is treated surgically, with subsequent postoperative radiation therapy. Surgery and radiation therapy, with their possible complications, are thus deferred until the patient clearly needs them[3,33,43,46] (Table 1).

Quality-of-Life Assessment in Neurooncology: Status Quo and Future

Once again, the most commonly used QOL measure in the neurosurgical literature is the KPS.[29] Primarily a physical outcome measure, it assesses four dimensions of QOL: ability to work, daily activity, self-care, and evidence of disease. Its validity and reliability have been questioned by some investigators.[26,38] One of the obvious errors in evaluating this instrument has been its use in patients with chronic disease other than cancer.[26] The main criticism of the KPS is its lack of sensitivity in patients with brain tumors who are relatively well (KPS > 80); this is a "ceiling" effect.[19,25,36,60] These functionally independent patients may show subtle cognitive deficits and other QOL dimensions because of tumor location and the effects of therapy. These deficits can only be detected with QOL measures that more specifically evaluate these functions in brain tumor patients.[24,69,70] On the other hand, several investigators have confirmed the interrater reliability[50,72] and the construct and predictive validity,[36,49,50,54] of the KPS and support its use as a valid measure of the key QOL dimension of well-being.[36]

SUMMARY

Certainly there is sufficient evidence that QOL measurement in neurooncology is an area deserving the same rigor and exacting precision as other research domains in our quest to improve the quantity and the quality of patient survival. Although it is understandable that measurement has gravitated toward a few standard measures such as the KPS, it is important to consider innovations in terms of utility-based, multidimensional, and disease-specific approaches that can perhaps offer more comprehensive, valid, and sensitive evaluations that are also more relevant to the concerns of our patients.

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