

## Quality of life in oncology with emphasis upon neuro-oncology

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### 1. ABSTRACT

Quality of life, as a science has been steadily gaining importance in both clinical practice as well as research. Despite major progress in the development of validated and clinically-relevant health-related quality of life (HRQOL) measures, we still face many challenges in bridging the gap between what we know and how to apply it in clinical practice: in making the transfer from the mere collection of QOL data to its utilization in improving patient outcome through interventional symptomatic therapy. This manuscript traces the development of QOL as a science to its potential utility in both clinical care and clinical research, as well as an outcomes measure. The emphasis has been placed upon quality of life in oncology with special attention to neuro-oncology.

### 2. INTRODUCTION

Although there is no consensus on the precise definition of health-related quality of life (HRQOL), to most people QOL means global life satisfaction. This feeling of global satisfaction is broadly affected by physical, mental and emotional health (HRQOL), as well as other personal, family, social, and educational factors.

During the past decade HRQOL as an outcome has become a national as well as an international priority. As a result we have witnessed an impressive emphasis upon QOL as a *patient-centered quality outcome* in oncology clinical practice and clinical trials in addition to the traditional *disease-centered quantity outcome*. Until recently, healthcare providers, as well as society at large, have considered the length of survival as the most important outcome for a patient with cancer. The last two decades have witnessed an increasing emphasis upon the impact of cancer and its treatment upon the patient's QOL, including the inclusion of QOL, in addition to survival, as one of the most important endpoints for approval of new drugs by the United States Food and Drug Administration (1,2).

Since 1989, when the Agency for Health Care Policy and Research began funding Patient Outcomes Research Teams (PORTs), outcomes research has taken on an unprecedented importance as the focus of this decade (3). In addition to the traditional outcomes that are usually addressed in traditional clinical trials, there has also been an increasing enthusiasm for the utilization of QOL as an

endpoint in economic outcomes (economic burden), and hence its utility in policy making and resource allocations.

The rationale for the current enthusiasm for clinical utilization of QOL include its utility:

- in therapeutic intervention
- in symptom control
- as an endpoint in clinical trials
- as an endpoint in outcomes research
- in a bio-psycho-social model of health practice and policy as an alternative to the current biomedical model
- possibly in charting future evidence-informed practice and health care policy and delivery
- in clinical ethical consultation, and
- in addressing the long-term effects of treatment upon HRQOL amongst cancer survivors.

This review article addresses the achievements as well as the current challenges and gaps that we face in the science and applicability of QOL in clinical oncology practice and oncology clinical trials, with emphasis upon neuro-oncology. In this review I use the word “challenge” to mean a quest or reason for better scientific knowledge and I use the word “gap” to mean failure to apply already gleaned knowledge.

However, the great enthusiasm for inclusion of QOL studies in clinical care, clinical trials, outcomes research, and clinical ethical consultation, needs to be balanced with the limited resources and the current low funding for QOL clinical trials. There is the necessity to move QOL research from the mere collection of data towards the utilization of this data to benefit the patient through interventional symptomatic therapy and evaluating the effects of such therapy upon QOL status.

Additionally, it is hoped that this paper will constitute a conceptual framework for widening the scope of ongoing research in quality of life as a field that interacts significantly with so many aspects of the decision making process, be it clinical, economic, humanistic or ethical.

Therefore, I will briefly review the potential contributions that the developing science of QOL could make to both oncology clinical practice and clinical trials, as well as to evidence-based health care policy: its significance in clinical oncology practice, particularly its consideration as a part of the process of the clinician's decision making and the value it has, despite the challenge it is, to improving the care provided by the health care worker.

- its value to the patient - the potential it has to improve patient-physician communication, and to increase patient's input (and satisfaction) into the decision making process.
- the value of QOL as a national priority in oncology clinical trials and the potential important role it has to either shift or modify our

current paradigm of heavy emphasis upon physical parameters and physical endpoints as inclusion/exclusion criteria.

- its contributions in the evaluation of current or new therapies.
- its role as a prognostic parameter and stratification factor in clinical trials
- its value as an outcome measure (clinical, economic, humanistic, and ethical outcomes) and its utility in physician accountability, policy making and resource allocation as a means of promoting and protecting health and HRQOL rather than as means for health care rationing

In addition to disease-focused outcome and pre-treatment neurocognitive status, pre-treatment QOL status could be an important prognostic factor for stratification in phase III clinical neuro-oncology trials.

I would propose that as clinicians caring for patients with complex symptoms of brain tumors for which we do not currently have a curative nor a life-prolonging effective therapy we need to shift our thinking from the linear outcome approach of morbidity and mortality to that of a multi-dimensional interventional approach, from the traditional clinical trials research that is disease-focused (cancer morbidity and mortality) to the evolving outcomes research that is both patient-focused as well as disease-focused. Quality of life implementation in decision making and its utilization in interventional symptomatic therapy can improve patients' quality outcome and satisfaction in a significant way and may additionally, as a possible independent prognostic factor, impact quantity survival as well (4-7).

It is not within the scope of this manuscript nor within the charge given to the author to cover the following very important areas of comprehensive patient care, namely, the science of cost-effective, economic outcome research, the vital importance of neuropsychology and neurocognitive contributions to comprehensive neuro-oncology care, or the important issues of end of life and palliative care in neuro-oncology clinical practice.

### 3. QUALITY OF LIFE: WHY IS IT IMPORTANT?

Since 1949 when the Karnofsky Performance Status (KPS) was introduced as a clinical scale to measure clinical performance of cancer patients (8,9), the evolution of QOL as an important science has culminated in its current establishment as a fundamental endpoint in cancer clinical care and clinical trials (10-12).

Two widely accepted aspects of QOL, its subjectivity and its multidimensionality, are best captured in its definition by Cella as: “The extent to which one's usual or expected physical, emotional and social well-being are affected by a medical condition or its treatment” (13,14). Because the subjectivity of QOL is influenced by the patient's expectations, emotional and affective experience, coping and adaptation skills, social functioning, and treatment satisfaction as well as by the dimensions of

physical, functional, emotional and family well-being, two patients with similar cancer diagnosis and receiving the same treatment under the care of the same oncologist can report two dissimilar QOL profiles.

The QOL analysis becomes important in describing the results of clinical trials when treatment options in commonly encountered neuro-oncological problems, as in patients with 1-3 brain metastasis, utilize new and expensive technology (e.g., standard whole brain radiotherapy with or without stereotactic radiosurgery) yield equivalency in traditional disease-focused endpoints of survival and time to disease progression but have disproportionate cost and/or adverse influence upon patient-focused endpoints of neurocognitive function or QOL. Moreover, QOL analysis becomes even more important when one of two comparable therapies yields superior quantitative survival with inferior QOL, or even shorter survival that might be preferred due to superior QOL outcome.

Another important role of QOL analysis in clinical trials is the ability of the pre-treatment QOL data to predict the likelihood of an objective response to treatment. This potential utility as a pre-treatment stratification factor in addition to changes in QOL during treatment could be predictive of survival (15,16).

As will be discussed later, QOL questionnaires often reveal somatic or psychosocial symptoms that initiate or facilitate provider-patient communication, which often improves patient's participation in the decision making process (patient autonomy) or that might lead to interventions that improve patient's overall well-being (beneficence) (17).

#### 4. QUALITY OF LIFE AS AN INTERNATIONAL AND NATIONAL PRIORITY:

QOL as a science has been rapidly evolving especially over the last 15 years with growing international interest and support for QOL assessment in both clinical practice and health services research, including health policy. This international effort has led to the emergence of the International Society of Quality of Life (ISOQOL) with its *Quality of Life Research* journal solely devoted to the furtherance of QOL science. The Medical Outcomes Trust was incorporated in Massachusetts in 1992 as a public service organization with a mission "of promoting the science and application of outcomes assessment, with a particular emphasis on expanding the availability and use of self- or interviewer-administered questionnaires designed to assess health and the outcomes of health care from the patients' point of view" (18). In 1994 a Scientific Advisory Committee was inaugurated by the Trust with the charge to establish review criteria for available self-reported-health and HRQOL instruments and to develop an instrument library or portfolio of translated instruments for outcomes measures that could be disseminated into international practice. In 1997, the Scientific Advisory Committee established criteria for translation, adaptation, and documentation required for instrument approval and

distribution. The initial criteria with their eight corresponding attributes were recently published following revision and expansion that addressed advances in modern test theory and the science of classical psychometrics (18). As pointed out in that publication, "the relative importance" of the eight attributes will differ from one intended use to another and an instrument that might work well for one study or population might not work well for another.

Individually and collectively the WHO, the National Cancer Institute (NCI) (19-22), the Food and Drug Administration (USA) (1), the national cancer cooperative groups (21), the American Society of Clinical Oncology (23,24), the Society for Neuro-oncology, and the European Organization for Research and Treatment of Cancer (EORTC) have made both commitment and contributions to the importance of moving forward the science of QOL in both clinical oncology and clinical trials.

#### 4.1. The WHO

The effort for the promotion of international health was first initiated by the International Sanitary Conference in 1851 to deal with the importation of the plague into Europe. The Pan American Sanitary Bureau was established in 1902, followed by the establishment of the Health Organization of the League of Nations in 1919. In 1945, at the suggestion of Brazil and China, efforts were initiated for the establishment of an international health organization which led to the drafting and the subsequent approval of the constitution of the WHO in 1946. The inception of the World Health Organization (WHO) on April 7, 1948 was a representative culmination of the international community's interest in promoting health. Since its inception, WHO has been giving worldwide guidance to fighting infectious diseases, cooperating with governments in providing health services, and discovering, developing and disseminating appropriate health technology, information and standards for human health (25).

At the time of its inception, the WHO defined health as "A state of complete physical, social and mental well-being, and not merely the absence of disease or infirmity" (26). The WHO has subsequently compiled the *Health Promotion Glossary* (25), published in 1998, which proposes unified international language for the definition of many health-related terms that will help in international communication and transmission of QOL activities and research. The definitions cited below are examples of unified QOL language for research publication and the international dissemination of its results:

Quality of Life: "Quality of life is defined as individuals' perceptions of their position in life in the context of the culture and value system where they live, and in relation to their goals, expectations, standards, and concerns. It is a broad ranging concept, incorporating in a complex way a person's physical health, psychological state, level of independence, social relationships, personal beliefs and relationship to salient features of the environment" (27,28).

The six domains of QOL that were identified by WHO constitute the “core aspects” of quality of life cross-culturally and are considered “complementary and overlapping”: physical (e.g. energy, fatigue), psychological (e.g. positive feelings), level of independence (e.g. mobility), social relationships (e.g. social support), environment (e.g. health care access), and personal beliefs/spirituality (e.g. meaning of life).

The WHO’s goal of promoting QOL has gained increasing importance in its global health promotion, especially amongst the elderly, the terminally or chronically ill, and the disabled. In collaboration with University of Edinburgh and 22 participating centers worldwide, the WHO has launched the WHOQOL-OLD project as “a measure to assess quality of life in older adults...in an innovative cross-cultural study of healthy aging [to examine] whether successful aging is culture-specific or whether there are common features which can be used to inform policy and decision making” (29). The WHO hopes that this study will result in QOL measure that can be used in a diverse variety of studies, including clinical intervention trials, with issues of crucial importance to QOL (29). In its 1997 Jakarta Declaration: Leading Health Promotion into the 21<sup>st</sup>. Century, the WHO identified, promotion through participation in decision-making process and empowering the individual as two of the strategies for which “there is clear evidence” for effectiveness in promoting its worldwide health goals (30).

- Health Promotion: “...is the process of enabling people to increase control over, and to improve their health” (25). A repeated goal in the WHO health promotion initiatives is to empower people through informed decision-making.
- Empowerment for health: “In health promotion, empowerment is a process through which people gain greater control over decisions and actions affecting their health” (25).
- Determinants of health: “The range of personal, social, economic and environmental factors which determine the health status of individuals or populations” (25).
- Health outcomes: “A change in health status...which is attributable to a planned intervention...regardless of whether such an intervention was intended to change health status” (25).
- Health status: “A description and/or measurement of the health of an individual or population at a particular point in time against identifiable standards, usually by reference to health indicators” (25).
- Health indicator: “A health indicator is a characteristic of an individual, population, or environment which is subject to measurement (directly or indirectly) and can be used to describe one or more aspects of the health of an individual or population (quality, quantity and time)” (25).
- Health policy: “A formal statement or procedure within institutions (notably governments) which

defines priorities and the parameters for action in response to health needs, available resources and other political pressures” (25).

### 4.2. The NCI

The “War on Cancer” was launched on December 23, 1971 by the signing of the National Cancer Act by President Richard M. Nixon (31). The years since the signing of the National Cancer Act have witnessed an impressive acceleration in the introduction of new technology and scientific discoveries. The “War on Cancer” has resulted in an impressive record of cancer survivorship leading the NCI to place in its “*Nation’s Investment in Cancer Research*” a top priority on improving treatment outcomes and quality of life: “Once almost uniformly fatal, cancer has become for many, a chronic illness, and for growing numbers, a curable disease. There are an estimated 8.9 million cancer survivors in the United States today. An impressive 14 percent of these individuals were originally diagnosed over 20 years ago.

“Cancer survival has risen steadily over the past three decades for all cancers combined.... As past and future advances in cancer detection, treatment, and care diffuse into clinical practice, the number of survivors can be expected to increase...

“While cancer survivors are living longer, we have limited knowledge and many questions about the health status, functioning, and quality of life for most of those who are post-treatment...

“What is clear is that most of our current treatments, although benefiting the patient overall, will produce some measure of adversity. In some cases, these effects can have a profound impact on survivors’ health and quality of life.” (19)

Although the initial goal of the 1971 National Cancer Act was to reduce the incidence, morbidity and mortality of cancer, the years since have witnessed an added emphasis by the NCI’s Cancer Therapy Evaluation Program (CTEP) upon quality of life as “of the highest priority” (32). Moreover, under the leadership of the NCI, a consensus conference was held in 1990 followed by a workshop in 1996 for the development and recommendation of methods for inclusion of QOL assessment in cancer clinical trials (20,21,33)

“*The Nation’s Investment in Cancer Research*” stresses the importance of discovering, developing, and disseminating knowledge regarding all aspects of cancer care and research (19). Although survivorship is currently a distinct rarity in patients with malignant brain tumors, survival is possible amongst a selected group of patients, especially the young with low grade tumors. Amongst these long-term survivors, the adverse effects of cancer treatment on the patients, their families, and caregivers remain poorly understood and inadequately documented. Knowledge of these effects is, however, vital if we are to help patients and their families make informed decisions about proposed treatments and how these may affect, in addition to their survival, their

future quality of life. Most importantly, unless effort is made to understand the nature and cause of long-term effects of treatment, the mechanisms that determine patient's response to cancer and its treatment, the pathophysiological basis for late effects and symptom development and relief, we will be unable to modify current treatment options or device interventional therapy that would avoid or effectively reduce these adverse effects. The rapid advancement of treatment modalities in neuro-oncology will undoubtedly make the future quantity survivorship a distinct possibility but not without associated late effects upon quality survival.

### 4.3. National Cancer Clinical Trials Cooperative Groups

The Cancer and Leukemia Group B was the first of the cancer cooperative groups to publish a 1987 report on quality of life and psychological distress and their relation to the extent of disease (34). In the last 15 years contributions from these groups have significantly added to our ability to laying the foundations of an infrastructure that would incorporate quality of life endpoints within traditional clinical trials and clinical research. Some of these contributions include:

- the demonstrable feasibility of conducting quality of life studies within the national cancer cooperative groups
- instrument development and psychometric testing
- methods of dealing with missing data points and strategies for improving compliance
- incorporating quality of life as an outcomes endpoint
- the accumulation of quality of life data has raised the need for cost analysis as an additional endpoint in cancer clinical trials (35).

As a participating clinical investigator of the RTOG for the last almost 20 years I am personally most acquainted with the initial RTOG efforts in implementing quality of life in neuro-oncology clinical trials and in the evolution of quality of life outcome as a component of the RTOG's outcomes model (35). The model consists of a previously proposed triad of economic outcome, clinical outcome, and humanistic or quality of life outcome (36).

Our group priorities were outlined in a recent RTOG grant as follows:

- minimize toxicities & improve QOL through consistent utilization of standardized panel of validated outcomes.
- identify interactions between clinical & humanistic variables
- assess interventions to improve these variables
- assess interaction between the triad of clinical, humanistic, and economic variables
- vigilance regarding compliance

In the succeeding section of this manuscript the term, "learning curve" will be used within the

RTOG as a model for development of quality of life studies in brain clinical trials.

### 4.4. The American Society of Clinical Oncology

In a recent editorial in its representative and prestigious journal the American Society of Clinical Oncology has eloquently summarized the journey of quality of life in clinical oncology and clinical trials. Having expressed disappointment "that there are relatively few examples of formal quality-of-life measurement that have influenced individual patient decision-making or treatment policies" the editorial went on to strongly "encourage research in the next step- the translation of QOL measurements into clinical practice to improve patient care" and a welcoming invitation "to publish such research" (24)

### 4.5. The Society for Neuro-oncology

The Society for Neuro-oncology has since its inauguration included quality of life as an integral part of its annual educational as well as scientific programs and encourages publication of QOL work in its official journal, *Neuro-Oncology*. "Quality of life presentations have been featured in the annual SNO Scientific Meetings since the Second Annual Scientific Meeting (October 31- November 2, 1997), and recognized by juried awards since the Fifth Annual Scientific Meeting (November 9-12, 2000) (37)

### 4.6. The European Organization for Research and Treatment of Cancer (EORTC)

The European Organization for Research and Treatment of Cancer (EORTC) contribution to the science of research and the clinical applicability of quality of life has been born of a long term and ongoing commitment of significant resources and manpower. The EORTC *Quality of Life Group* was created in 1980 to "advise the [EORTC] *Data Center* and the various cooperative groups on the design, implementation and analysis of QL studies within selected phase III clinical trials." (38). The unique cultural mix with professionals of wide range multi-discipline backgrounds (more than 2,000 clinicians in 350 medical institutions in 35 countries), languages, cultures and geography places the EORTC in a unique position for research in methodology, development, translation, dissemination, and implementation of reliable quality of life instruments that are applicable across a wide range of cultural settings as outcome measures in international clinical cancer trials. The *EORTC Quality of Life Unit* has also established guidelines for the development and translation of core-specific as well disease-specific modules, in addition to reference values manual (39-50). The multi-cultural, discipline, and linguistic input into the development of its QOL instruments, places the EORTC in a very unique position to ascertain that the competent linguistic translation does not sacrifice the values that are unique across many cultures (38).

## 5. QOL IN ONCOLOGY PRACTICE AND CLINICAL TRIALS:

### 5.1. Significance and challenges

Since the early 1980's, and since utilizing the World Health Organization definition of QOL (26), quality of life research and applicability in clinical oncology has

steadily been gaining momentum and importance. However, despite great enthusiasm and major progress there remain major challenges and gaps in the cost-effective applicability of quality of life in both cancer clinical trials as well as clinical oncology. Additionally, the science of guideline development for authors and peer reviewers has been lacking.

I will review the current status of quality of life in Oncology, and more particularly in neuro-oncology. We who are interested in quality of life as a discipline in neuro-oncology can learn valuable lessons from the journey that quality of life research has taken in the practice of clinical oncology and in the design of oncology clinical trials. One lesson we can hopefully learn is how to overcome some of the challenges and how to bridge some of the gaps that currently stand in the way of translating quality of life research into benefiting our patients without laying an increasing demand on already scarce and limited resources.

The American Society of Clinical Oncology has recognized patient quality of life (QOL) assessment as second in importance only to measuring patient survival (23). There has also been a call from QOL researchers that QOL be implemented as an end-point in oncology clinical trials (10). Despite that heavy emphasis upon the importance of QOL in cancer clinical care & research, we remain unable to define the best QOL constructs and how best to implement and utilize such an assessment towards lessening patient suffering and improving patient outcome. (51).

The FDA is currently redrafting its guidance on the clinical trial endpoints to be considered in the approval of new cancer drugs and biologics. The suggested endpoints include overall survival, endpoints based on tumor assessments (disease-free survival, objective response rate, time to tumor progression, time to treatment failure), endpoints involving symptom assessment (specific symptom endpoints (time to progression of cancer symptoms, time to progression of symptoms, time to onset of symptoms, composite symptom endpoint) and biomarkers. (2). In a letter to the FDA regarding the proposed endpoints, the Cancer Leadership Council, a patient-centered coalition of national advocacy organizations, advocated for the use of HRQOL, as a patient-reported measure, as “basis for supplemental approvals or other means of communicating this important information in the product labeling” (52). The “FDA’s current thinking” on HRQOL as one of the patient-reported outcomes is currently under consideration and is expected to be published in a final draft any time soon (2).

Despite a plethora of literature dealing with QOL in cancer, published clinical trials dealing with QOL have fallen below good standards of scientific reporting. (39, 53) There remain many barriers to the successful implementation of QOL by clinicians. The term QOL is both broad in its applicability and imprecise in its meaning (54). There remain considerable gaps between the research literature and the clinician, gaps in explaining the clinical

significance of QOL parameters, and gaps in defining unified guidelines for QOL assessment and interpretation. (11) Additionally, despite studies showing the contrary, researchers and clinicians alike often view the use of QOL assessment as an unnecessary cost and an additional burden to both patients and clinicians. (55). In many cases poor implementation of QOL assessments has resulted in lack of demonstrated usefulness (11, 56).

This is another challenge to be overcome. In the mid 1980s, during the infancy years of the development of quality of life as a discipline, it was observed that one of the major barriers to the effective implication of quality of life in clinical practice and research was the development of a serious gap in collaboration between those who had developed the quality of life measures, namely the social scientists, and those who sought to apply these measures in practice, namely, the clinicians. In the mid 1990s, a “similar gap of communication and information” was identified “this time between clinicians and social scientists on one hand and economists, health care administrators, and policy makers on the other” (57). Subsequent symposia held in the United States and by the EORTC (57,58) have increased both the awareness and the collaboration amongst clinical oncologists, social scientists, economists and others regarding the need for economic as well as quality of life outcomes to be part of ongoing clinical trials and research. Yet the current “ gap of communication and information ....between clinicians and social scientists on one hand and economists, healthcare administrators, and policy makers on the other” will need to be closed (57).

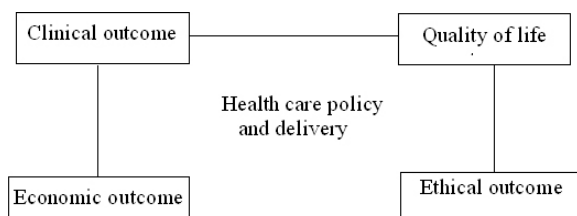
The subjective and multidimensional nature of QOL, in addition to its evolutionary rather than static nature, add unique challenges to its measurement:

- the QOL questionnaires should preferably be answered by the patient rather than by an outside observer (family or provider proxies)
- the QOL instruments should be validated, reliable, and multidimensional
- successful linguistic translation of a QOL instrument might be a cultural failure if it falls short of transmitting unique cultural dimensions that vary across different cultures.
- On one hand, they should be disease-specific, covering specific illness, symptoms profile, specific types of treatment, as well as sensitive to changes related to the specific disease and its treatment.
- On the other hand they need to be generic illness instruments in order to provide important cross-disease and cross-clinical trials comparisons

### 5.2. Economic Challenges: How Quality of Life as an outcome measure can help towards evidence-based healthcare policy

Likening our current healthcare system to the human body, current vital signs raise serious concerns about escalating cost and future affordability. If our economy is to remain globally competitive, action needs to be taken to curtail the current rate of rising healthcare costs,

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**Figure 1.** A model for health care's stewardship and accountability.

which are projected to be about 17% of our GDP by 2007 (59). Our slowly ailing health care system needs healthcare providers' input towards a solution that would emphasize the combination of accountability, cost analysis, and clinical outcomes research that focuses on other outcomes in addition to those of traditional morbidity and mortality (60,61). This would need to be done with ethical competence so that we stress that the primary focus of such research is not to ration health care dollars but to stress the urgent need for safeguarding the resources necessary to support basic and clinical science research as the surest hope for finding curative therapy for cancer. Support for effective research and application of the science of QOL as an outcome measure in both oncology clinical care and oncology clinical trials in addition to or in lieu of some current physical/clinical outcome measures could be part of that solution. QOL outcome is an important measure in the proposed model of the ECHO triad for outcomes research: economic outcome (cost), clinical outcome (scientific), and humanistic outcome (quality of life). ( 35,36).

In neuro-oncology, as in other fields of clinical medicine, unless optimal or total care is being measured we cannot be sure it is being delivered. In the United States there exists an urgent need for an alternative model of assessment of our healthcare outcomes. The United States leads the world in both per capita health care expenditures and percentage of the gross domestic product dedicated to health care spending (62). Additionally, we have the world's most technologically advanced health care system. Yet, not counting the underinsured, 44 million Americans, mostly young, working poor, and minorities, have neither health care insurance nor routine access to health care. This creates a serious disparity in our delivery of health care and anxiety among Americans about the future of healthcare affordability and access. The 2003 Employer Health Benefits Survey from the Kaiser Family Foundation reports, whereas 9% of Americans are worried about being the victim of a violent crime or a terrorist attack, 33% are worried about future affordability of health care insurance, 26% are worried about prescription drugs affordability and 25% are worried about the quality of health care (63).

In this paper I make reference to the triad outcome model (economic, clinical, humanistic outcomes) that was initially proposed by Kozma *et al* in 1993 (36). A similar model has been adopted and is being developed by the Outcomes Committee of the Radiation Therapy Oncology Group (RTOG) (35). Both models have a potentially serious drawback in that neither one

incorporates ethics into their outcome models. The reality is that unless we do something to curtail the escalating cost of healthcare, our economy might not enable us to invest effectively in clinical and basic science research. The current paradigm of relying solely on the "quantity survival" of physical and clinical parameters in assessing the effectiveness of treatment has proven to be inadequate to justify the continual escalation of cost. A new paradigm is needed in our search for a more cost-effective delivery of health care and that paradigm must include the humanistic outcome (quality of life), the economic outcome (policy regarding cost affordability and resource allocation and health care delivery) along with the traditional clinical outcome. Since these outcomes could have serious and unfair implications for the elderly, the disabled, and the poor, the social implications of such an outcomes model must be judged by society's ethical standards.

Although the problem of cost escalation and access shortage is on a national level, cooperation between physician leadership and local and state health care organizations is vital for a successful alternative of our current healthcare system. One should never underestimate the collective powers of practicing healthcare providers in helping to mold such an alternative model.

We can no longer afford to ignore the fact that rising health care costs will eventually paralyze our employers' ability to compete in a global economy. At times of dwindling finances for research support, such as we have been experiencing in the United States, it is essential that we re-examine the traditional way health care interventions are being evaluated. There is a desperate need for an alternative assessment of the cost effectiveness of our current healthcare policy and system delivery. One such alternative model could be the model suggested in Figure 1, which is my self-imposed physician accountability, which has evolved over the last 17 years of my clinical practice and has been inspired by parents, teachers, colleagues, as well as the literature (2, 36).

Another could be the process model proposed by Martin and Stocker (64) who proposed a process model for improving health outcomes by utilizing QOL assessment in:

- identification of health problems,
- evaluation of new treatments,
- formulation of treatment guidelines and health policies,
- the delivery of optimal care in practice, and
- the assessment of outcomes, healthcare research, and practice.

Health outcomes research should ideally evaluate the human, economic and scientific effects of health care practices upon the individual as well as the society. Because of the inherent limitations in the traditional decision-making model, the insufficiency (despite importance) of physical/clinical findings alone as a measure of an intervention's impact (65) and because of the rising societal, ethical and medical concerns about

escalating cost, access and quality of care, outcomes research is becoming an indispensable discipline of medicine in seeking to understand the impact of health care practices and interventions and to develop recommendations towards better health care policy and delivery. Kozma, *et al* proposed the Economic, Clinical, and Humanistic Outcomes (ECHO) model for outcomes as a preliminary, theoretical, and more comprehensive model for medical decision making and for potential optimization of allocating health care resources (59). Quality of life outcomes in clinical oncology practice as well as in oncology clinical trials are an example of combining a humanistic measure with the economic and scientific measures for a more comprehensive evaluation of health outcomes

### 5.3. Challenges in designing successful QOL studies

“Without research” said the Honorable Paul G. Rogers, sponsor of the National Cancer Act of 1971, “there is no hope”.

Despite decades of experience in designing HRQOL studies, many questions and challenges still surround their successful design and objectives:

- How could we implement QOL as an end point in clinical trials? How to select QOL as an appropriate outcome, how to select frequency of assessments, how to handle missing data, and what would be the QOL value in comparison to the traditional prognostic factors such as age, grade, MRI, KPS, neurological function, etc.
- What role should the pharmaceutical industry have in study design, funding, data ownership, interpretation, and publication? This is a vitally important ethical issue that can influence the scientific independence of quality of life research, especially in phase II studies.
- Is it feasible or even possible to design a QOL study that, like neurocognitive assessment, would be able to separate the effects of brain tumor from the effects of its treatment! The challenge in designing such studies in brain tumors is that the study needs to be “narrow” so as to capture the traditional “lobar syndromes” & so wide that it cannot miss any of them as innocent bystanders of treatment effects (e.g. radiation effects on the contra-lateral hemisphere). Presently there exists no successful model in neuro-oncology, except in the case of prophylactic cranial therapy in ALL that would enable us to modify clinical practice as a result of utilization of retrospective QOL data in the successful separation of the effects of cancer from the effects of its treatment. This is true in clinical practice whether we are dealing with tumor location (right versus left hemispheric, lobar versus multi-focal, supratentorial versus infratentorial), tumor histology or grade (low versus high grade), treatment modality (single versus combination therapy) prophylactic brain radiotherapy in patients with small cell lung

cancer versus paraneoplastic neuro-psychiatric syndromes

- How to choose the appropriate QOL tool: organ-specific, histology/grade specific, global QOL module, treatment specific, or symptom-specific and what beneficial role does each play in the design of successful interventional therapy?
- How do we account for the effects, if any, upon quality of life of financial and psychosocial factors, depression, pain, anxiety, concomitant use of drugs and systemic co-morbidities such as risk factors for small vessel disease (hypertension, age, diabetes, heavy smoking), and how do we account for the impact of the serious and debilitating effects of steroids (fatigue, weight gain, disfiguring features, insomnia, emotional lability, hypertension, gastric/bowel perforation, glucose intolerance, myopathy, fluid retention, psychosis) upon QOL?
- The utilization of control groups in the study of QOL in cancer patients has remained an unexplored field with inherent challenges of its own. Potential “control groups” for consideration could include patients with systemic cancer without CNS involvement, patients with degenerative dementia, and other acquired and traumatic injuries.

Direct involvement of a member of the healthcare team in discussing the QOL aspect of clinical research with the patient and/or his/her proxy, will result in improved patient participation and satisfaction, and will significantly improve the quality contributions made by the patient's proxy. Among patients with chronic illness, concordance is found to be better for the physical domains than the psychosocial domain (66). Psychosocial factors modify the impact of disease on individual patients (67) Aside from biological factors, psychosocial factors are of possible prognostic value in terminally ill patients (68). Moreover, QOL assessment is viewed as an independent prognostic variable in cancer survival (4,5).

Some of the major obstacles to successful QOL research within the cooperative cancer trials and its applicability in clinical practice are:

- Lack of consistency in the selection of already validated QOL tools. This constitutes a serious barrier to building a cost-effective database, flattens the learning curve towards successful interpretation and implementation of the data, and makes across study comparisons a sure impossibility.
- Employment of “cut and paste” approach in utilization of already validated tools in an effort to keep down the cost of clinical trials. Such approach seriously sacrifices the internal consistency and validity of QOL tools.

RTOG 91-14, the first RTOG brain “QOL study”, was published by Choucair *et al* in 1997 (69). This study was undertaken to prospectively test the feasibility of



performing quality of life evaluations and collecting this data within the RTOG. The data provided information regarding the patients' day-to-day functional abilities that were not provided by routinely used means, such as KPS and the neurological function scale. The serial mini-mental status exam, although insensitive as a measure of cognitive function, proved to provide greater sensitivity to patients' differences in neurological status and a potential preference as an eligibility criteria. Although institutional participation was only 40%, the participation rate had significantly risen to well over 80% in subsequent brain quality of life studies (69). The study concluded that further testing needed to be done to determine whether the pre-radiation treatment MMSE scores would add prognostic significance beyond that of traditional prognostic factors and whether quality of life data could be utilized in timely interventional symptomatic therapy to improve quality survival. Unfortunately, subsequent studies within the RTOG failed to build upon this early experience. The inconsistent utilization of quality of life measures within the RTOG brain studies had in the past hindered the development of the QOL data base necessary for the latter goal and furthermore made it impossible to do cross study comparisons. Because of limited funding for quality of life studies we have not been able to test the feasibility of conducting quality of life studies within RTOG phase II clinical trials. While quality of life outcomes are important in equivalency phase III studies, they are important in toxicity phase II studies in deciding whether effects upon quality of life would qualify the study to move into a phase III trial. Again without consistent building of a quality of life database, which is vital for cross study comparisons, such decisions could not be made for the lack of scientific evidence. The interested reader will find the article by Bruner *et al* to be an excellent source for tracking the evolution of quality of life within the RTOG oncology clinical trials into an outcomes variable. (35).

- Failure to prospectively select study endpoints that take into account both the available resources and the potential beneficial return to the patient.
- Study designs that do not prospectively take into consideration a plan for data collection and how to account for and deal with missing data points.
- Despite the value placed by the United States Food and Drug Administration upon quality of life in the drug approval process, yet there continues to be a serious lack of agreed upon standards of scientific reporting of quality of life in clinical trials (39).
- There is a lack of model for cost/benefit analysis of new therapies and the role that quality of life plays in that model. The successful RTOG model proposed by Bruner *et al* could be a major step in that direction (35)
- Primary end points (MRI, TTP, PFS, DFS, toxicity) in Oncology clinical trials are disease focused. There is an urgent need to quantify the "total" patient experience as quality-adjusted life years by combining conventional (disease-focused) end points with (patient-focused) QOL end points (70).

- There is a virtual absence of QOL studies that deal with interaction and correlations between the clinical and the humanistic variables.
- There is a lack of consensus as to the acceptability of proxy raters (71). This subject will be discussed later under a separate heading.

There is the misconception that the process of data collection is seen as an additional burden upon the patient & the physician that usually does not translate into benefit to the patient. Comprehensive cancer care is aimed at treating both the cancer as well as the patient. Interventional symptomatic therapy offers the patient symptomatic relief even when the cancer is resistant to primary therapy. For the successful implementation of interventional symptomatic therapy the healthcare provider will have to address patient's symptoms and concerns that are usually not captured in standard clinical evaluations or in the evaluations of new anticancer drugs and protocols (69). Anxiety, depression, insomnia, and fatigue constitute major cancer co-morbidities that are responsive to therapeutic intervention. How the resultant symptomatic improvement (except for the successful management of cancer pain) affects patient's overall QOL remains the subject of much needed future research (72). Since co-morbidities such as depression, pain, anxiety and fatigue negatively impact cognitive function and are risks for poorer quality of life, and since their impact upon quality of life can be modified, interventional symptomatic therapy can be individually customized to deal with these co-morbidities (73-75).

There is a need to collect baseline and follow-up QOL self-assessment responses in parallel with the traditionally established clinical/physical outcomes so we can formulate a better idea of which aspects of QOL is both feasible and important to conduct in the care of brain tumor patients, which aspects of QOL (patient's perspective) best correlate with the disease-focused (physician's perspective) endpoints and hopefully take us a step closer towards answering the call from the NCI for improving the QOL of cancer survivors (19)

One of the key issues in designing successful QOL studies is to make sure the economics and clinical outcome questions harmonize with the humanistic, quality of life question that is being asked. Patient's experiences with brain tumor are subjective. Patient's formulation, interpretation, and reaction to these experiences are multidimensional and are influenced by multiple determinants (subjective personal values, expectations, social, psychological, spiritual, and financial circumstances, neurological deficits, etc....). Since brain cancer influences multiple domains of function (physical, cognitive, social, emotional, spiritual) in patient's life, the fulfillment of patient's expectations is thus multidimensional. "Total QOL" measures the total impact of disease and its treatment upon the patient, upon the family, and upon the society. It also measures the impact of the primary and the secondary interventional therapy upon the same (76). HRQOL assessment, on the other hand, does not measure these determinants, but rather

scientifically measures the manifestations (functional outcomes and symptoms) of these determinants. Quality adjusted life years (QALYs) is a method of analyzing QOL that compares, in a single measure, the impact of health interventions, both clinical decisions and public health programs, as well as new medical technologies on both the quantity as well as the quality of life. Since all life years are not equivalent, QALYs, which adjust life years by their quality, could be used as a measure of physician's accountability for clinical outcome (scientific), cost-effectiveness analysis (economics) and quality of life. One of the limitations to the use of QALYs is that they are disease-specific and as such cannot be used to compare one group of patients with another. Moreover, they tend to be restrictive when it comes to aspects of QOL; despite the established important effects of social, work, and psychological satisfaction upon QOL, QALYs take into account only those aspects of life that are related to health, most typically physical function (77).

### 5.4. Keys to Successful Design of QOL Studies

For a QOL study design to be successful in overcoming many of the obstacles that currently stand in the way of implementing QOL in clinical practice a consideration should be given to combining disease-focused outcomes with patient-focused outcomes:

- Utilizing a mix of already validated QOL tools (disease-specific module in addition to general cancer module) that are weighted in favor of patient's perspective, especially in the following settings: a) treatments that yield equivalent survival but have differing toxicities, b) treatments that minimally impact survival, c) cancer prevention studies, d) late effects of treatment, e) interventional symptomatic treatment, and f) evaluation of quality of care (78)
- Preserving the standards of functional assessment that are weighted in favor of physician's perspective.
- Statistician's review, input and approval of the study before its submission to the IRB.
- The study should compliment rather than interfere with providing the patient with the best possible cancer care.
- It is imperatively important that the QOL question(s) be prospectively identified. This is especially important in randomized clinical trials when comparing standard treatment to newer promising regimen, comparing two survival-equivalent treatments with different disease-free survival, or comparing two survival-equivalent treatments with different toxicities or cost (78).
- A detailed plan with specified individual accountability for each member of the research/data management team for explaining the study and its potential benefits to the patient (79).
- A detailed process plan with individual staff accountability for compliance with data collection and reasons for missing data points.
- Clear elaboration of the study endpoints taking into consideration different groups of patients (e.g.

different histologies, different treatment plans, and different survival patterns) with a commitment towards continuity and future building of a successful database. e.g.:

- ❑ Exploring the feasibility of collecting longitudinal QOL data in phase III clinical trials enrolling patients with primary brain tumors utilizing already validated QOL self-assessment measures.
- ❑ Multi-phase plan for working towards the implementation of QOL as an end-point in outcomes. The QOL tools to be used should be applicable for future use and for cross-study comparisons in outcome and cost analysis studies.
- ❑ Reporting descriptive statistics of QOL global and subtest scores by established standard clinical factors by time for different groups.
- ❑ Reporting the predictive correlations between the change in QOL scores, the change in performance scales [KPS, Zubrod, Neurological Function (NFS)], the neurocognitive and the Mini-Mental State Examination (MMSE), and the MRI for patients with the same as well as with different brain tumor histologies and grades.
- ❑ Explore the impact of interventional symptomatic therapy on the above parameters.
- ❑ Clear delineation of the exclusion criteria and whether proxies should be allowed for patients who are unable or unwilling to complete the QOL questionnaires.
- Comparison of validity and internal consistency between patient's self-rating of quality of life and clinician-rated, disease-focused traditional endpoints.
- Utilization of quality of life measures with increased sensitivity would result in need for fewer patients in order to create a difference.

### 5.5. Challenges in applying QOL study results into clinical practice

Challenges stand in the way of full application of QOL into clinical practice. Amongst these is the lack of a unified definition of QOL, the need to move from mere data collection to the utilization of the data to benefit the patient through interventional symptomatic therapy, the delineation of the role QOL plays in understanding the effects of cancer versus the effects of its treatment, and how to effectively incorporate QOL as an end-point in clinical trials (10,23).

The evolving importance and progress of QOL research in neuro-oncology and its significant contribution to improving the patient's overall outcome, is being hampered by the lack of the necessary resources, especially limited funding. As a consequence, many clinicians and researchers believe that the investment of limited resources in routine QOL studies is of questionable

benefit except in selected patient population (e.g. the young with low grade tumor and projected long term survival).

One of the chief challenges is moving from the collection of descriptive QOL data to the scientific utilization of the data to benefit the patient through modifying known adverse side effects of the treatment, the implementation of interventional symptomatic therapy, the utilization of QOL studies in separating the effects of the tumor from the effects of its treatment, and how to employ QOL research in economic analysis studies.

Manual collection and entry of data points into a database is quite laborious and resource consuming. Unless the QOL data collection and utilization in clinical practice and clinical research is reimbursable or funded, its use in routine clinical practice places a significant strain upon physician's resources. However, Wright *et al* demonstrated that QOL data collection could be made easy, inexpensive and cost-effective, and readily interpretable in a large number of patients attending oncology clinics. They field-tested the feasibility and compliance of QOL measurement in oncology practice employing a computer touch-screen system using for QOL instruments the EORTC QLQ-30 and the Hospital Anxiety Depression Scale. In the second of two studies all 1291 patients attending outpatient oncology clinics were offered QOL assessment as part of clinic routine during a period of 12 weeks. The overall compliance (median 100%; mean 70%) was retained over multiple visits, and despite the difficulty encountered in data collection on the wards (sicker patients) in comparison to the clinics, nonetheless data collection and storage in the computer system was excellent (98% in one center) (80).

Two basic challenges stand in the way of interpretation and clinical utility of HRQOL research data. First patient compliance with QOL measures declines over time leading to a serious challenge in the meaningful interpretation and, hence clinical utility, of HRQOL studies due to missing data. This is particularly true in patients with malignant brain tumors due to the coexisting neurocognitive deficit. The other challenge results from "response shift". "Response shift" refers to a change attributable to changes in the meaning of that construct, as understood or experienced by a respondent [and] can reflect change in the respondent's internal standards of measurement (scale recalibration), change in respondent's values regarding the importance of component domains of quality of life (reprioritization), or redefinition of meaning of quality of life itself (reconceptualization)" (81). This "response shift" phenomenon was not taken into consideration in the design of the current generation of quality of life measures (82).

It is a fact that without explanation from healthcare workers about the importance of QOL measures, patients might perceive the completion of QOL questionnaires as being unnecessary for a successful visit with their healthcare provider. Detmar and Aaronson demonstrated the effective utilization of QOL as a facilitator in clinical oncology practice without increasing

consultation time (40). Despite this data there is a continual physician reliance on their analysis of the patient's QOL erroneously assuming that patients find such measurement to be intrusive and that a clinician can readily and correctly discern patient's QOL without formal QOL assessment.

It is a fact that in addition to its established utility in clinical trials as principal or subsidiary endpoint, quality of life when utilized in clinical practice enhances the interaction between physicians and patients, uncovers symptoms, especially anxiety and depression (41), and other issues of importance to the patient and to patient outcome that might otherwise not come to the attention of the clinician (69).

It is a fact that psychological factors modify prognosis and impact disease. For this reason looking at the accuracy of physician estimates and relevance of spiritual well-being (SWB) to QOL becomes important in clinical practice. Fisch *et al* found clinician estimated QOL-impairment matched the level of patient-derived QOL correctly in ~ 60% of the cases and the accuracy of clinician estimates was not associated with the level of SWB. However, in a subset analysis of the inaccurate estimates there was an association between lower SWB and clinician underestimation of QOL impairment. They also found strong relationship between SWB and QOL but no significant association between self-assessment scores and marital status, education level, performance status, or predicted life expectancy (83). Unfortunately, spiritual dimension (meaning of illness, hope, uncertainty) is missing from FACT-G and most similar QOL instruments

In transforming the results of QOL research studies into clinical application the study design needs to address several of the above mentioned gaps and overcome the challenges that currently exist in the application of QOL tools into clinical practice. There is a need to use a combination of QOL measures that reflect both patient perspective as well as physician perspective. Traditional QOL measures have come under criticism because they tend largely to be reflective of the patient's perspective, whereas standard clinical & functional parameters tend to be dominantly reflective of the physician's perspective. In current clinical practice it is often the clinician who interprets the collected information with greater emphasis on the more readily defined endpoints, such as physical functioning, and less emphasis on the subjective changes in QOL. The physician thus becomes a proxy for the patient's perspective.

Slevin *et al* (84) demonstrated unequivocally that doctors could not adequately measure patients' QOL. Utilizing as instruments KPS, Spitzer QOL evaluation, Hospital Anxiety and Depression Scale, and Linear Analogue Self Assessment Scale (LASAS), questionnaires were filled by patients, their doctors and their relatives acting as proxy. The results revealed the following:

- There was considerable variability in results between different doctors

- Doctors' scores rarely explained more than 30% of the variability in patients' scores
- There was much greater variability in the doctors' scores on LASAS than in those of the patients
- The correlations between the doctors' different scores on KPS were higher than the correlations between doctors' and patients' scores

The KPS demonstrated greatest reproducibility than any of the other measures that were filled out by the health professionals.

Many questions and challenges still surround the clinical applicability and objectives of QOL studies in cancer clinical trials:

- How to reconcile, correlate or establish internal consistency between the clinician's and the patient's contributions to the QOL evaluations.
- What are the ultimate objectives of doing QOL studies as part of clinical trials and how to move from the mere data collection to the implementation of the data in successful targeted interventional therapy and how to measure the impact of such interventional therapy upon improvement in QOL?
- How to define a clinically significant change.
- How to develop models that would evaluate the influence or inner relationships of pre-existing or illness' unrelated social, cultural, psychological, and economic issues upon QOL

### 5. 6. Proxy Assessment in HRQOL

Because of associated neurocognitive deficits, nowhere in the practice of clinical oncology and research is the utilization of proxy of more importance than in the practice of neuro-oncology. Although this is especially true in patients with primary and secondary brain tumors, it is of great or equal importance in patients with non-metastatic or paraneoplastic neurological complications of cancer.

The subjective nature of QOL would necessitate that the patient be the primary source of information in its assessment. Moreover, one of the challenges in utilization of proxy is the proxy's inability or limitation to reflect two very important aspects of patient's experience with cancer as a chronic disease; namely patient's affective and emotional response to cancer and secondly patient's adaptation to cancer over time. Utilizing a proxy informant about patient's QOL becomes necessary when the patient because of cognitive impairment, age (the very young or the frail elderly), sickness or language barrier finds it impossible to provide that self-assessment. Such utilization might be considered a better alternative than excluding the patient from participating in a clinical study. Exclusion of such patients from clinical trials could, in addition to being ethically unacceptable and discriminatory against patients with disabilities, be the source of a major data bias and hence its interpretation, acceptability or generalization. Of more importance, elimination of such proxy could lead to elimination of this group of patients from participation in clinical trials that could be of a beneficiary outcome to the patient. Proxy

assessment is of vital importance in caring for patients with chronic suffering whose suffering could go untreated either because they have adapted to it or who for reasons of stoicism or anxiety tend to minimize it (85,86).

In studies of patients with chronic neurological or non-neurological disabilities or diseases, acquired or degenerative, Sneeuw *et al* reported that 20 – 50% would need their HRQOL to be assessed by proxy (87). One of the challenges in proxy assessments is that ratter's response, be it from significant others or from the health care providers, underestimates patient self-reported HRQOL (88), with agreement and reliability being best for relatives and lowest for health care providers, with tendencies for proxies' overestimation of impairment and underestimation of HRQOL with the pattern reversing on pain assessment. (89). In a study on measuring agreement between proxy and patient responses to HRQOL measures in clinical trials, Weinfurt *et al* found that the level of agreement tended to diminish with the severity of the illness (90).

Among cancer patients, there is a better general agreement between patient self-assessment and proxy on symptoms and domains of health that are more concrete or observable with proxies' tendencies for worse rating on the subjective domains (91). Kommer, *et al* reported on the use of significant others as proxy ratters for the QOL of patients with brain tumors (92). Their study included 103 patients with either recently diagnosed or recurrent brain tumor, 75% of the proxies employed in the study were spouses, and 22% were relatives; they utilized the EORTC QLQ-C30 and the brain-specific module QLQ-BCM. They found 60% of the patient and proxy scores were in "exact agreement with more than 90% of scores being within one response category of each other". Although the authors observed less agreement and more pronounced response bias for the patients with confusion, they recommended the need for future studies to evaluate the reliability and validity of proxy HRQOL evaluations in patients with brain tumors.

Pickard and Knight proposed a conceptual framework for understanding proxy perspectives (71). Proxy assessment could be given as supplementary to the patient's self-assessment with the proxy's response hopefully convergent with the patient's perspective as if the proxy is projecting him/herself into the "body and mind" of the patient (proxy-patient perspective). Or it could be given as a substitute to the patient self-assessment (proxy-proxy perspective) knowing purposefully that such a substitution would be divergent from the patient's perspective. Whether it is the first type of proxy that result in, what Pickard and Knight call the "inter-ratter gap" or the later type which they call "intra-ratter gap" their conceptual framework constitutes a forward thinking about how to reconcile these gaps in utilizing proxy HRQOL in clinical trials.

### 6. QOL AND TREATMENT DECISION-MAKING

The last two decades have witnessed a movement towards an increasing emphasis on personal and

**Table 1.** Significant discrepancy between patient's perspective (PP) and physician perception of patient's perspective (PPPP) in decision making

Decision making	PP	PPPP
Active	20%	29%
Shared	63%	39%
Passive	17%	32%
Concordance	45%	-

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individual rights that have made significant impact upon the practice of clinical medicine and the design of clinical trials. There has been an increased emphasis upon patient autonomy, informed consent, and patient-focused outcomes in addition to the traditional disease-focused outcomes (23,78). In addition to the traditional principles of medical ethics (autonomy, beneficence, nonmaleficence, and fairness), HRQOL, in addition to medical indications, patient preference, and contextual features, is considered to be very important in the analysis that leads to a successful clinical ethical consultation. (93).

Simultaneously the last two decades have witnessed an increasing emphasis on quality of life as an end-point in cancer clinical trials leading to increased consideration of patient's opinion and his/her preferences in the process of decision- making and enrollment in cancer clinical trials (33,94,95). With the proliferation of new and expensive anti-cancer agents and new strategies for intensifying dosage and combination of treatment modalities there has been an increasing demand to deal with the increasing toxicity and to inform the patient upfront of its potential impact upon his/her quality of life. This has led to the inclusion of patient's preferences in the decision-making process, especially, when alternative therapies provide equivalent disease-focused outcome. Although patient's satisfaction is increased by the efforts to improve communications it is not clear if or how these efforts impact treatment decisions (96). It has also been repeatedly emphasized that quality cancer care should include treating the patient as well as the cancer and to include "quality of life as a companion to the more time-honored question of the quantity of life." (97)

Research into patient preferences for increased role into the treatment decision-making process has been on the rise, especially in clinical oncology (98,99). Social scientists have for a long time been exploring the meaning and the key components of a successful shared decision-making process (100).

Both, the American Society of Clinical Oncology and the United States FDA have included benefit to QOL, in addition to survival, as an endpoint for consideration and approval of new anti-cancer drugs (1,23). Discussion with the patient about the potential impact of new anticancer treatments upon his/her quality of life will undoubtedly empower the patient in the decision making process and makes it more likely that the patient and the physician will reach a true concordance in the final treatment choice. (101-103) Patient's autonomy, as a vitally important principle of medical ethics, cannot be

intelligently exercised by the patient without knowledge of the treatment alternatives and their respective quantitative as well as qualitative, outcome. Moreover, such discussion is likely to overcome some of the shortcomings that are currently being experienced in the consenting process for patient participation in cancer clinical trials. According to The New York Academy of Science "we learn that physicians' policies and practices toward informing cancer patients differ somewhat, but remain ignorant as to the much more relevant issue of the patients' own wishes." (104,105).

According to the NCI's "*Nation's Investment in Cancer Research*" cancer is increasingly becoming a chronic illness amongst an increasing number of cancer survivors (19). This is especially true among good risk, long-term surviving neuro-oncology patients. Amongst patients with chronic non-cancer disease, Arora *et al* reported that although 69% of these patients would rather leave the treatment decision with the physician yet patients with higher level of education, younger age and female gender prefer more active role in the choices of treatment options and their impact upon their quality of life (106).

Among women with breast cancer, Degner *et al* reported 22% would like to select their treatment, 44% would do so in collaboration with their physician, and 34% would rather delegate that decision to their doctor. However, only 42 % of those patients reported having achieved their preference and 15% felt being "pushed" into the decision by their physician. (107). Bruera *et al* reported significant discrepancy between patient's perspective (PP) and physician perception of patient's perspective (PPPP) in decision making with only 45% concordance (108) as shown in Table 1.

There is evidence that suggests that shared decision making may result in improved patient satisfaction and lead to better compliance as well as health outcome (101,102). Additionally, some investigators have reported that patient self-rated health is a predictor of survival among patients with advanced cancer. (109).

The scientific documentation of physicians' attitudes towards QOL issues in neuro-oncology care has comparatively been lagging behind that of other fields of clinical oncology. This should come as no surprise since prospective scientific documentation of QOL outcome in phase II and III neuro-oncology clinical trials has been sparsely published. Without knowledge of the spectrum of QOL outcomes it would be very difficult to assess how neuro-oncologists interpret or apply QOL data in their practices or use it in consenting patients enrolling on clinical trials. Currently no data exist as to how physicians and patients would utilize QOL data in clinical neuro-oncological care or how relevant or interpretable current data would be to both patients or physicians.

Further studies are needed to guide us towards the informed inclusion of the effects of treatment upon QOL in the consent document of cancer clinical trials. Unless special effort is made to capture this data in phase II

studies and evaluate its interpretability and relevance its inclusion in phase III studies would be a challenge. Since it is the patient that “suffers”, the physician that “interprets” and the society that “pays” it becomes important that the deliberations leading to the final draft of a clinical trial keep the input and the connectiveness of these three parties in mind

### 7. INCLUSION OF QOL IN DEVELOPING PRACTICE GUIDELINES

In addition to rising interest amongst clinicians and researchers in the applicability of QOL to clinical practice there has also been a rising interest amongst insurance and government agencies regarding the cost accountability of various anticancer agents (11,51)

In no branch of clinical oncology is the study of cost (economics) and quality of life (humanistic) in relation to clinical outcomes (scientific) more relevant than it is in neuro-oncology. Because of overall poor prognosis, the lack of long-term effective treatment despite major advances in expensive technology, and because the target organ is the seed of cognition, personality, emotions, behavior and functional control, the cost of care and its impact upon quantity as well as quality of survival becomes vitally important. Although quality of life is exceptionally important to any patient afflicted with any illness, it is especially so when we deal with the two extreme subgroups of patients with brain tumors: the elderly with poor prognosis despite the best available treatment and the young with good prognosis but potential long-term effects of treatment.

Another “gap” exists between what we know from research and clinical trials and what we do in clinical practice (110). Using clinical guidelines that are derived from evidence-base medicine in oncology practice could be both helpful as well as very challenging. Although data derived from randomized clinical trials constitute the best evidence-based medicine yet gaps exist between the research evidence and the care of the individual patient (111). Nonetheless, following clinical practice guidelines still overall produces consistently better patient outcomes and do help in creating a consistently higher quality of care in comparison to practice based on anecdote (112).

It has been proposed by Calman that quality of life could be viewed as the “size of the gap” between the patient’s expectations and reality. (113). Likewise, a “purist” economist could see in the utilization of relatively ineffective yet advanced technical and expensive treatment for malignant brain tumors a serious “gap” between investment and return. This is one of the reasons why true outcomes research must bring together the humanistic dimension (quality of life), the scientific dimension (clinical research and outcome) and the economic dimension, and subject them to ethical considerations in making recommendations regarding practice and policy guidelines.

Practice guidelines in neuro-oncology are either not comprehensive or are limited in their clinical applicability to the traditional care model of heavy reliance upon physical/clinical endpoints (114), are ignored in clinical practice, or are contradictory as in the case of using radiosurgery in treating single or extensive brain metastasis (115-117) Moreover, terminal patients may not be influenced by evidence and consequently might choose to ignore the evidence in favor of continuing ineffective treatment.

Despite their lack of universal or consistent popularity among practicing physicians, the clinical usefulness of QOL-centered practice guidelines could be significantly enhanced in bridging the “gap” between the escalating costs of high technology health care and dwindling health care dollars by helping healthcare plans and policy makers identify, relative to each individual patient, which treatment regimens are unproven, disproved, or highly experimental (112).

Since the effectiveness of most experimental, phase II, and end of life therapies is currently being measured by the quantity of life (survival) adding quality of life evaluations, especially to phase II studies, would be another step towards not only minimizing the existing “gap” between economics and clinical effectiveness without lowering standards of care but will, to the contrary, improve patients’ end of life quality survival by shifting the focus from primary therapy towards the more needful interventional symptomatic therapy and palliative care and support. Brenner *et al* proposed a model of “proximal-distal continuum” of multiple health outcomes measures that might be beneficial to consider, especially when considering interventional therapy. (118). Proximal outcomes (signs and symptoms) are clinical indicators of disease and are most powerfully and directly influenced by effective interventional therapy, whereas distal outcomes (role functioning, general well-being) tend to be “more removed from the illness per se and are usually the product of a multitude of non-illnesses or external factors” and as a result tend to be less influenced even by very effective interventions (119).

It is important to reiterate that in the design of a quality-of-life study that the QOL question being asked be very clear and that the appropriate QOL tools be utilized, remembering that general cancer modules tend to be inferior to symptom-specific modules and alone are not reflective of the data that could be obtained from disease-specific modules (120).

Physicians’ cooperation and accountability are vital to the successful implementation of practice guidelines in order to not only ensure the quality of care delivered according to practice guidelines derived from the best evidence medicine but also to make sure, by assessing the quality of life as an outcome parameter, that the gap between the clinical, humanistic and economic outcomes is being bridged based upon sound scientific [and ethical] principles (121).

Moreover one highly positive outcome of physician proactive involvement in the development and implementation of evidence-based medicine is the possibility that the rate of insurers' support for and participation in clinical trials would increase. Well conducted, high quality clinical trials, coupled with basic science research, hold the greatest promise in improving cancer treatment and in advancing us closer to a cure. However, the current participation of patients in such clinical trials is by far the major hindrance in the timely and speedy delivery of their useful (positive or negative) results. Less than 5% of adult cancer patients participate in clinical trials (122). Although the major barrier cited to participation is concern about insurance denial (123), yet a closer look at the published data would be enlightening:

- In a Harris Interactive survey of 5,900 cancer patients only 14% of the survey sample were aware of clinical trials (123).
- According to a report from the United States General Accounting Office, many insurers, despite policies excluding payment for "experimental" therapies, already cover the costs of patient care for participants in "qualifying" clinical trials (124,125).

Although it is debatable whether enrollment in cancer clinical trials leads to improved outcomes (126) yet because cancer clinical trials have been proven to be cost-effective (127) federal and state policy makers, as well as private insurers now support reimbursement of routine medical care in clinical trials (122).

### 8. ROLE OF QOL AS A PROGNOSTIC FACTOR

As pointed out earlier in this manuscript, pre-treatment QOL data can predict the likelihood of an objective response to treatment and that pre-treatment as well as during-treatment QOL could be of predictive prognostic utility in some systemic cancers (15,16).

Current prognostic factors and criteria of evaluating tumor response to treatment fall short of explaining different outcomes for patients with comparable tumor-focused prognostic factors. Several generic instruments (e.g. KPS, Activity of Daily Living, MMSE) attractive for their simplicity and ease of use in clinical care have been used to study QOL in patients with brain tumors. As pointed out by Meyers and others, it is of critical importance in designing quality of life trials that we keep in mind the significant differences between measures of performance status, activities of daily living, quality of life, and neurocognitive performance (56,69,128,129).

There is a need to explore other prognostic factors (e.g. molecular markers, neurocognitive function, quality of life) and how they correlate with each other and with current traditional prognostic factors. There exists a preliminary evidence of relationship between genetic markers and colon cancer patients' quality of life (130). The correlative relationships between prospectively

gathered longitudinal QOL data in parallel with traditional radiological, clinical, and neurocognitive data would need to be explored in such a manner that in addition to building QOL data base the data could be used towards better documentation and understanding of treatment effects and maximizing patient's QOL through more implementation of interventional symptomatic therapy. Currently there exists no data in the clinical trials literature that has prospectively evaluated baseline or longitudinal QOL changes during treatment as an independent prognostic factor in patients with brain tumors. Studies addressing the prognostic power of QOL in patients with systemic cancer have revealed conflicting results: either no independent prognostic correlation of baseline QOL parameters in patients with nonmetastatic breast cancer (131), independent prognostic factor in univariate analysis of elderly with lung cancer (132), independent prognostic factor in univariate but not in multivariate analysis in patients with advanced bladder cancer (133), and independent prognostic predictor in multivariate analysis in patients with esophageal cancer (134).

## 9. SPECIAL CONSIDERATIONS OF QUALITY OF LIFE IN NEURO-ONCOLOGY

### 9.1. Background

Gliomas account for more than 50% of primary brain tumors with almost 80% being malignant grades III and IV and the remaining 20% are dominantly low grade II (135). Because of poor prognosis despite multi-modality primary treatment, options for secondary treatment at time of recurrence offer limited success: rarely resulting in a better than partial response or at best a short-term disease stabilization. The deleterious effects of the invasive tumor upon cognitive and personality function are usually compounded by the effects of treatment upon the normal function of the remaining brain leading to a serious impairment of the patient's HRQOL. Thus for patients with malignant brain tumors quality survival becomes of paramount importance and must be taken into consideration when weighing options of treatment for recurrent disease, including participation in phase II clinical trials. For many reasons, this importance unfortunately has not been reflected in the published quality of life literature.

Anxiety, depression and emotional distress can become disabling at any time during a patient's journey with cancer. Because of their significant prevalence amongst cancer patients and because they could easily go unnoticed in busy oncology practices that are focused on acute issues, the American Cancer Society and the National Comprehensive Cancer Network have collaborated on publishing guidelines that would help clinicians and patients recognize the "red flags of excessive distress" and how to treat them (136):

- Overwhelmed by fear, despair or hopelessness
- Sadness that may interfere with cancer treatment,
- Unusual irritability and anger
- Failure to cope with fatigue, pain or other symptoms

- Difficulty with concentration, decision making, and memory function
- Thinking constantly about cancer or death
- Problems with insomnia, appetite
- Feeling worthless and useless
- Questioning the once comforting faith and religious beliefs
- Conflicts that seem impossible to resolve.

These symptoms, which alone can significantly affect thoughts, feelings and daily function, become of added importance in patients in whom such functions have already been compromised by the effects of brain tumor or its treatment. Despite their prevalence, the clinical relationships between fatigue, depression and existential issues and QOL in patients with brain tumors remain poorly understood and inadequately documented. Although we do not currently understand the pathophysiological correlations of these symptoms to cancer, yet a better understanding of these co-morbidities will undoubtedly lead to better interventions, better coping and better QOL. Co-morbid psychosocial problems undoubtedly augment the negative effects of tumor-related focal neurological damage and the treatment-related more diffuse damage.

Existential or spiritual issues, fatigue, depression and emotional distress have not been delineated in patients with primary or secondary neuro-oncological diseases and disorders. Spiritual issues have been shown to correlate with patients' general QOL to the same extent as physical wellbeing and independently of other possibly confounding variables (137). This positive correlation has been felt to be secondary to a more active coping style inspired by the patients' spiritual beliefs (138).

It is also important to recognize the double-edge effects of steroids upon the function and QOL of patients with brain tumors. Although steroids can significantly improve symptoms of increased intracranial pressure yet they cause a variety of emotional and behavioral problems: labile affect, anxiety, depression, mania, insomnia, and aggression.

Longitudinal studies of documenting the spectrum of neuropsychiatric problems and their relative contributions to QOL in patients with brain tumors are lacking. Pelletier *et al*, in a cross-sectional, questionnaire-based survey of 73 patients with primary brain tumors, most of whom had been extensively treated in a tertiary cancer center with radiation therapy, chemotherapy or both, reported although 38% scored in the clinically depressed range on the Beck Depression Inventory-II, yet in this sample of patients the overall QOL scores were no different than in a reference sample of brain tumor patients. Although 57% of the patients were classified as "struggling" with existential issues, yet their scores on the existential subscale of the McGill Quality of Life were comparable to those of a reference sample of cancer patients undergoing care (139). Despite the interrelatedness of the scores on depression, existential issues, fatigue and emotional distress, Pelletier *et al* concluded that none of

them correlated with length of survival, that the most important independent predictor of QOL was the presence of depressive symptoms, and that of all demographic and disease-related variables, patient employment status was strongly related to depression, fatigue and existential issues.

The development of the science of HRQOL in neuro-oncology has suffered from the same shortcomings as it has in general oncology. These shortcomings, both underdevelopment and under utilization, are reflected in the sparse literature on the employment of HRQOL as an endpoint in randomized neuro-oncological clinical trials.

Moreover, many earlier studies of quality of life in patients with brain tumors have erroneously equated the non-patient self-reported KPS, activity of daily living, the neurocognitive status, and the MMSE with quality of life. Although the KPS has proven to be a strong prognostic factor yet it has serious limitations as a poor substitute for patient's QOL. Some of these limitations are:

- It is unidirectional & blind while QOL measures are multidimensional and subjective
- It reflects no patient input or perspective (no subjectivity)
- It is heavily physician-biased (objectivity)
- It is possibly lateralization & lobe dependent (highest w/ R-frontal lobe tumor location) (69,140,141)
- It has a poor correlation with and is a poor "proxy" for QOL or Cognitive function (142).
- In highly functioning patients with malignant glioma (KPS 90-100), there is an inverse relationship to age but no relationship to QOL or well-being indicating that KPS lacked sensitivity in this group of highly functioning patients. (128). On the contrary, Giovagnoli *et al* reported no significant relation between age and KPS in disease-free brain tumor patients (140)
- Relationship between KPS and QOL is insignificant among relatively healthy patients with malignant brain tumors and KPS 90-100 (128)
- 75% of patients with brain tumors maintain KPS  $\geq$  70% for one year followed by rapid decline in functioning immediately before death (143)

Osoba *et al*, utilizing the EORTC QLQ-C30 and the BCM-20, studied the effects of neurological dysfunction on health-related quality of life. They reported that in comparison to patients with recurrent disease and to those with KPS of 50-70 newly diagnosed patients and patients with KPS 80-100 had significantly better physical, role and cognitive functioning, and global QOL and less fatigue, visual disorder, motor dysfunction, communication deficit, bilateral leg weakness, and bladder dysfunction. They demonstrated good correlation between deteriorating neurological status and decline in cognitive, physical, role, emotional, and social functioning and with global QOL (144).



The mini-mental status exam (MMSE) has also been used as part of or a substitute for QOL or neurocognitive status. When we first reported the importance of combining MMSE with other self-assessment questionnaires in evaluating the QOL of patients enrolled on RTOG phase III brain tumor clinical trials (69). The implication was never to use it as equivalent to or a substitute for formal neurocognitive evaluation or QOL. Having been aware of its poor correlation with early mental decline, the intent was to use it in parallel with other longitudinal data and as such to evaluate its prognostic power, if any, over time. The MMSE, used alone has several limitations:

- It provides limited assessment of neurocognitive domains and has limited correlation with early decline in cognitive function & QOL and is especially insensitive to frontal lobe lesions.
- It does not avoid memorized learning
- It does not differentiate between primary effects of tumor and secondary effects of treatment on cognitive function.
- We do not know if it has any significant role in differentiating between cognitive effects of primary brain tumors, metastatic brain tumors, the remote effects of systemic cancer, or the effects of treatment.
- Insensitive to focal brain lesions.
- Insensitive to mild or early cognitive decline.
- Lacks well-established specificity/sensitivity.

Despite these limitations, the experience of utilizing the MMSE within the RTOG brain protocols has demonstrated that pre- & post-treatment scores correlate with survival (69,145,146). Likewise, in a report from the North Central Cancer Treatment Group, Brown *et al* found that, in a multivariate analysis, the abnormal ( $\leq$  or = 26) baseline MMSE was a strong predictor of poorer 5-year progression-free and overall survival (27% vs. 60% and 31% vs. 76% respectively with  $p < 0.001$ ) in a group of adults patients with low grade glioma who were prospectively randomized to a low versus high dose localized radiotherapy (147).

These multiple limitations make the MMSE a very poor alternative to neurocognitive assessment in patients with primary or metastatic brain tumors and seriously limit its utility in randomized trials in evaluating the impact of therapeutic alternatives upon quality of life as an outcome. Despite multiple arguments against the inclusion of neurocognitive measures in patients with brain tumors, their feasibility and utility have been well demonstrated in both clinical trials involving patients with brain metastases (146,148) as well as in patients with primary brain tumors (149). Meyers *et al* (149) reported their institution's experience with cognitive function versus QOL as predictors of early progression as measured by MRI in patients with primary brain tumors. Using validated neurocognitive battery, QOL and ADL at intervals coinciding with MRI, they demonstrated that deterioration in neurocognitive scores preceded disease progression on the MRI by 6 weeks whereas median time for QOL

deterioration was not achieved and for ADL was 43 weeks long after MRI-documented disease progression. This finding has a significant implication for current clinical practice of emphasis upon the traditional neurological exam (particularly the motor exam) and the KPS.

Giovagnoli *et al* studied the effects of neurocognitive impairment upon QOL, as measured by FLIC, in long-term survivors of supratentorial malignant brain tumors with different stages of disease and treatment. Although the symptom-free group (18 patients) showed less impairment than the symptomatic group (18 patients) with clinical and radiological evidence for recurrence, yet the patients in the symptom-free group showed sub-clinical cognitive deficit (attention span, memory, word fluency) with impaired QOL as well as more depression and more fatigue than healthy controls. The study pointed out that even sub-clinical neuro-cognitive deficit impairs quality of life (150). In other studies, cognitive impairment has been reported to be most serious in patients with disease recurrence and to be significantly impaired in all patient groups in comparison to controls. (140).

After treatment for primary brain tumors, psychological morbidity is associated with high levels of physical disability and cognitive dysfunction but not with tumor grade (151). Moreover, anxiety and depression have been reported to be highest among the patients undergoing chemotherapy (140)

In another study, quality of life was also negatively affected by depression, anxiety, and KPS in glioma patients with stable disease (no clinical and no radiological signs of recurrence or radio-necrosis after surgery, radiation and chemotherapy treatments) but only by anxiety in control patients with chronic neurological disorders. (152).

In the same study (152) Giovagnoli reported no relationship between QOL as measured by FLIC and the histological type of the tumor (suggesting that either disease status, which was homogenous in this patient group, is more important than intrinsic tumor characteristics, or that FLIC may be more patient-focused than disease focused), surgical procedure (biopsy versus resection), tumor location, age, gender, or marital status. Moreover, there was no significant difference in QOL, ADL, mood and cognitive scores between the study group with brain tumors and the control group with chronic neurological disorders (152). The finding that disease status is more important than histology in determining quality of life in patients with stable disease cannot be generalized because the study population (14% had GBM) was not representative of the patients with brain tumors. Other studies have demonstrated higher QOL ratings on FLIC in patients with right hemispheric and anterior location of brain tumors (140) which might be explained by lack of insight or less likely by relatively less serious cognitive impairment for that location in comparison to left hemispheric location. Among highly functioning glioma patients QOL is reported to be negatively affected by the presence of bilateral disease,

chemotherapy, performance status, divorced status and female gender (153).

In order to study the effects of “disease burden” on health-related quality of life, it is important to keep in mind the primary effects of tumor as well as the secondary effects of treatment (76). The tumor usually causes focal neurological deficits (aphasia, focal sensory or motor deficit, seizure, visual field loss), generalized deficits secondary to increased intra-cranial pressure (headaches, ataxia, sleepiness, drowsiness, fatigue, difficulty with concentration, neurocognitive impairment, nausea and vomiting) and neuropsychological deficits (personality changes, mood disturbances, impulsiveness). Accordingly these deficits have been classified as impairment (the traditional measure most sensitive to objective outcome parameters because of its potential reversibility in response to treatment), disability (impacts KPS and ADL), or handicap (impacts patient’s quality of life) (129,154). Whereas impairment is most sensitive to tumor response and as such is important as an outcome measure in treatment evaluation, disability and handicap are of most importance to the patient.

Since most patients with Glioblastoma multiforme are elderly, it is important to point out that the evaluation of QOL in the elderly patient population is filled with challenging problems (155):

- High rate of illiteracy in comparison to the younger patients
- Cognitive deficits that make comprehension of QOL questionnaires difficult
- Higher incidence of comorbidities in comparison to the younger patients. This makes it difficult to separate out the impact of comorbidities upon QOL from those of the cancer and its treatment
- QOL instruments have not been validated in the elderly population
- Selection bias will invalidate the meaning of the data if only high function elderly were selected for participation.
- Older age is associated with underreporting of significant depressive symptoms (156).

In a comprehensive search of the English literature published between 1981 and 2001, Efficace and Bottomley found that HRQOL was being neglected as an endpoint in neuro-oncology clinical trials. They found only 5 randomized clinical trials in adults with gliomas that addressed patient’s self-reported measures of QOL (157). These trials suffered from poor design in assessment methodology, instrument administration and reporting. One of the trials was funded by industry, one enrolled patients with low grade glioma, and none utilized HRQOL as a primary endpoint (157). In a phase II study in GBM patients who were treated at first relapse by either temozolomide or procarbazine, Yung *et al* reported significant progression-free survival at 6 months as well as improvement in seven of the scores on EORTC-QLQ-30 in favor of temozolomide (158,159).

### 9.2. Quality of Life in Patients with Low Grade Glioma

Quality of life is of paramount importance in the life of every individual, whether in health or in illness. HRQOL as an endpoint in clinical trials becomes even of more importance in patients with short-term survival and for whom the effects of one treatment may be a better option than another because of differential impact upon their QOL. Because of the relatively better survival, better insight, and better neurological and neurocognitive function in patients with low grade glioma, quality of life has unique challenges and becomes a very important end point over a long period of time in comparison to those with higher grade gliomas. Moreover, quality of life as an outcome becomes of increasing importance as to the patient’s ability to participate in the decision making process.

The best approach to the management of low grade glioma has remained highly controversial. Neither early resection nor early treatment with radiation therapy has proven to improve survival nor do we fully understand their effects upon quality of life or cognitive function. Clinical trials have not only failed to come up with “best approach” for the management of these patients but have also failed to show survival benefit from early radiotherapy or to demonstrate dose-response relationship thus arguing in favor of deferring surgical or radiation intervention. (44,45,160).

Taphoorn *et al* reported two retrospective studies in patients with low grade glioma assessing the quality of life and cognitive function in both studies. In the first study (46) patients were treated with surgery and focal radiation therapy and none of the patients has any clinical (median KPS  $\geq 80$ ) or radiological signs of tumor recurrence. Cognitive function was impaired in all patients. There were high scores on depression, anger, fatigue, and tension and low scores on vigor as well as significant personality changes, which in some patients had led to social isolation. The cause of neuropsychological and cognitive deficits was difficult to assign to the tumor or its treatment. The second study (47) compared 2 groups of long-term survivors both with biopsy-proven low grade glioma and without clinical or radiological signs of tumor recurrence, one receiving focal radiation and the other without any treatment, to a group of long-term survivors of low grade hematological malignancies. Although none of the survivors had significant neurological impairment (preserved KPS) and although the two groups did not differ significantly in cognitive or affective deficits from each other, yet they both suffered significantly compared to the control group thus arguing that radiation therapy did not impact quality of life. This study also demonstrated the dissociation between cognitive and affective dysfunction and the KPS.

Kiebert *et al* on behalf of the EORTC Radiotherapy Cooperative Group reported on the quality of life from a prospective phase III study randomizing patients with low grade glioma to a low dose (45 Gy/5 weeks) versus a high dose (59.4 Gy/6.5 weeks) radiation therapy. There was no survival difference but the patients in the lower dose arm had less symptom burden and better

functioning level thus arguing in favor of the lower dose arm in terms of lesser cost and lower adverse effects at no decrement in survival (48).

Reijneveld *et al* evaluated cognitive function and quality of life in 2 groups of patients with low grade glioma, one with suspected but deferred diagnosis and the other with histological proven diagnosis to a healthy control group. Although cognitive function and quality of life were worse in both patient groups compared to controls, yet the patients with deferred diagnosis performed better on both measures in comparison to the patients with the proven diagnosis and there was no significant difference between them in terms of future uncertainty, thus arguing in favor of “wait-and see” approach (48).

### 9.3. Quality of Life in Patients with High Grade Glioma

Because of the short length of survival, lack of effective treatment, and the invasive nature of these tumors that seriously impact neurocognitive function, quality of life in these patients becomes of especial importance when comparing two phase II treatments that might be survival-equivalent but with varying impacts upon quality of life. The literature contains several randomized studies that address issues of quality of life and neurocognitive function in patients with high grade gliomas. These studies give us idea regarding the possible study questions to address in prospective clinical trials.

Neurobehavioral status and quality of life were compared between two groups of cancer patients (newly diagnosed high grade glioma and lung cancer) and healthy controls (50). HRQOL was significantly worse in both cancer groups compared to healthy controls, neurological and neuropsychological functions were worse in the glioma group than in the lung cancer group, but neurocognitive function was impaired in all the glioma group. Anticonvulsant therapy negatively impacted memory function. The extent of resection was not related to neuropsychological function

In a randomized study of patients with GBM (standard radiation versus stereotactic radiotherapy plus brachytherapy boost), using the Sickness Impact Profile as a quality of life measure, Bampoe *et al* found no significant difference between the two groups (161).

Weitzner *et al* found that quality of life in patients with primary brain tumors was most affected by the extent of tumor involvement and that performance status, female gender, divorced status, being unable to work, undergoing aggressive treatment, age, grade, and time since diagnosis did not influence quality of life. (162). The limitations imposed upon this study by the relative small number of patients with varying grades of primary brain tumor would dictate the need for a randomized trial to confirm some of its findings, especially the impact of ongoing treatment upon HRQOL.

## 10. SUMMARY

In summary, when it comes to employing quality of life in oncology clinical practice and clinical trials, “the

question is no longer whether...but what is the most reliable and practical means of obtaining these essential data” (84). Some of the challenges that need to be addressed could be summarized as follows:

- **Applicability:** It is very important that we move from the mere collection of data to the utilization of the data to benefit the patient in assessing the needs of the patient, improving the patient-physician communication, and empowering the patient’s autonomy in decision-making, especially in the choice between two survival-equivalent treatments but differing impact upon HRQOL.
- **Consistency and Continuity:** lack of consistency and continuity creates serious problems in cross-study comparisons across various clinical trials, ineffectively escalates their cost, and hinders policy decisions. Additionally, “cut and past” approach results in loss of validity and internal consistency of already validated QOL measures.
- **Study Design:** Well-designed clinical trials come at a cost. Multiple endpoints arise from utilizing multiple quality of life domains (general and disease-specific), repeated assessments over time, and multiple treatment arms (163). As much as possible multiplicity of outcomes should be avoided. Only those questions should be asked that could translate into therapeutic or policy benefit. There is also a need to watch the language: there is difference between patient’s nonself-reported neuro-cognitive domains, activity of daily living or performance status, and the patient’s self-reported quality of life (129). There is also a need for an early and clear delineation of the data collection process, accountability for and how to deal with missing data points, establishing guidelines for the frequency of administering QOL measures, and for establishing guidelines for reporting QOL research (164).
- **Resources:** Because creating a data-base is effort, time, and money consuming, and because of the reality of the current low priority of funding for quality of life studies within cancer clinical trials it becomes vitally important that we make every effort to maximize the outcome, e.g. targeting special population groups (e.g. limiting inclusion to “good risk” patients with GBM) and narrow the scope of data points without sacrificing the quality of the study.
- **Understanding the pathophysiology of symptoms,** their impact upon quality of life, and how to measure the impact of interventional symptomatic therapy upon quality of life.
- **Identifying which quality of life parameters are common to all cancer**
- **How will the prognostic panel for patients with brain tumors look like with the addition of neuro-cognitive function, quality of life, and molecular markers as inclusion or stratification criteria, and how would the humanistic quality of life**

parameters correlate with the traditional clinical/physical parameters. There is a need to prospectively duplicate and expand upon the single institution experience of Meyers and Hess (149).

- Delineate the role of quality of life studies in Phase II trials.

It is important for providers who deal with HRQOL to realize that there is more to an individual's global health than health care, that HRQOL is not a proxy, but a subset of a patient's global QOL, and that health status alone, without health values attached to it, is not reflective of HRQOL. There is a real need to increase our efforts in involving the clinician in our goal to establish the reliability of HRQOL data relative to the physiological data for it is in this involvement that we increase the sustainability of our goal.

### 11. APPENDIX

Listed below are commonly used QOL measures with a brief description of the characteristics of each. For an excellent comprehensive list of the commonly used quality of life and symptom measurement scales, please consult reference (165).

#### EORTC BCM-20 (42)

- 4 multi-item scales (future uncertainty, visual disorder, motor dysfunction, communication deficit)
- 7 single items (HA, seizure, drowsiness, hair loss, itching, weakness of both legs, diff w/ bladder control)
- explores distress
- showed internal consistency, test-retest correlation, and discriminate validity for tumor recurrence and KPS score

#### Functional Assessment of Cancer Therapy-Brain (FACT-BR) (166)

- Self-administered, modular instrument that measures HRQOL in brain tumor patients
- It is composed of a core instrument FACT-G and a disease-specific (brain tumor) subscale
- 58 questions that yield a total of 8 scores: 5 subscale scores, a QOL score, a score for the brain cancer module, and a total FACT-BR score.
- 4 functional scales (Physical, emotional, social, cognitive)
- Content validity, test retest correlation and internal consistency

#### EORTC QLQ-30 (43,167)

- Self-assessment questionnaire
- 5 functional scales (physical, role, cognitive, emotional, social)
- 6 single items (dyspnea, insomnia, anorexia, constipation, diarrhea, financial impact)
- 3 symptom scales (fatigue, pain, nausea/vomiting)

#### FLIC (functional living index-cancer) (168,169)

- Investigated in 837 cancer patients
- Self administered multi-dimension visual analogue scale divided into 7 intervals (maximum score 154) higher scores reflect greater perceived well-being
- 22 questions that explore physical well-being {5 questions}, emotional {7}, social {2} and occupational aspects {3}, and drug side effects {nausea, 2}, family situation {3}
- Demonstrated appropriate content and structure validity

Concurrent validity with KPS and state-strait anxiety inventory STAI: strong relationship between FLIC and KPS, as well as between FLIC and anxiety and depression rating; thus validity of FLIC in assessing both the physical as well as the emotional aspects of life. However, there have been no prospective published studies demonstrating its applicability in neuro-oncology.

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