Neuro-Oncology Practice

Neuro-Oncology Practice 2(1), 2–5, 2015
doi:10.1093/nop/npv002

Health-related quality of life and other clinical outcome assessments in brain tumor patients: challenges in the design, conduct and interpretation of clinical trials

Linda Dirven, Terri S. Armstrong, and Martin J.B. Taphoorn

VU University Medical Center, Department of Neurology, Amsterdam, Netherlands (L.D., M.J.B.T.); The University of Texas Health Science Center at Houston, School of Nursing, Department of Family Health, Houston, Texas (T.S.A.); The University of Texas M.D. Anderson Cancer Center, Department of Neuro-Oncology, Houston, Texas (T.S.A.); Medical Center Haaglanden, Department of Neurology, The Hague, Netherlands (M.J.B.T.)

Several outcome measures are available to evaluate the benefit of a specific treatment strategy in clinical trials for brain tumor patients. Traditional outcome measures are progression-free survival and overall survival as well as the radiological response assessed on magnetic resonance imaging (MRI). Equally important, patient-centered outcomes are available that focus on outcome measures reflecting patient functioning, symptoms, and health-related quality of life (HRQOL).

Patient-centered outcome measures may also be denominated as Clinical Outcome Assessments (COAs) as used by the US Food and Drug Administration. COAs can provide additional information about the beneficial and adverse effects of a treatment, which may assist patients and their caregivers, together with their physicians, in making informed health care decisions about the best possible treatment for the individual patient while taking into account patient and tumor characteristics, clinical condition, and preferences.[1]

Several COAs are available and include patient-reported outcome (PRO) measures, clinician-reported outcome (ClinRO) measures, observer-reported outcome (ObsRO) measures, and performance outcome (PerfO) measures (see Table 1). ClinROs such as physician measurement of neurologic functioning and PerfO measures such as neurocognitive testing are perceived as objective measures of a patient's functioning, while PROs such as HRQOL, symptom burden, and (instrumental) activities of daily living reflect the patient's perspective[2] and are therefore subjective by definition.

Information on survival only is insufficient for determining the so called "net clinical benefit" of a treatment strategy. The impact of the disease and its treatment can only be identified by additional multidimensional assessments.[3] Thus, to determine the net clinical benefit of a treatment, it is important to include both traditional and COA measures.[4] However, methodological barriers may hamper the generation and interpretation of COA data, which we will introduce below.

How to Reconcile Clinical Outcome Assessment Data and Survival

Although treatment aims to prolong survival with maintenance or improvement of functioning, these outcomes may be conflicting. A trade-off discussion may arise when (i) survival is prolonged in the experimental treatment arm compared with the control arm but functioning is significantly worse, or when (ii) survival is worse but functioning is significantly better in the experimental treatment arm.[4] It is difficult to decide what to opt for in these situations. Therefore, the question arises whether quantity and quality of life should be analyzed separately or if both outcomes should be integrated into a single outcome measure. Are there currently methods for doing this? How should the gathered data be analyzed and interpreted?

Design of a Clinical Trial: Which Clinical Outcome Assessment to Select and When to Assess

The selection of COA for a clinical trial may depend on the specific research question; the objective could be to determine the immediate toxic effects of a specific treatment, the long-term effects of this treatment at the moment immediate toxicity effect has faded,[5,6] or to understand the impact of a treatment while the disease is controlled. The choice for a COA should therefore be based on the expected and specific adverse effects of treatment as well as understanding the impact of the disease. Equally important is consideration of the timing of the COAs, keeping in mind the anticipated adverse effects of the treatment and feasibility of assessment.

An example of the importance of timing assessments in relation to treatment is a clinical trial investigating the addition of procarbazine, lomustine, and vincristine (PCV) chemotherapy to radiotherapy in anaplastic oligodendrogliomas.[7] In this study, the timing of the completion of HRQOL questionnaires is assumed to have attenuated HRQOL scores, especially on the nausea/vomiting scale.[8] More specifically, patients were required to complete HRQOL questionnaires after the completion of a PCV cycle. However, the HRQOL questionnaires refer only to the preceding week and not to the complete 6-week cycle duration. Since nausea and vomiting are commonly caused by either lomustine administered on day 1 or procarbazine administered on days 8–21 of the treatment cycle, most severe toxicity effects had already faded by the time HRQOL was measured. Therefore, the timing of the

Table 1. Definition of Clinical Outcome Assessment (COA) and the 4 subtypes

Clinical Outcome Assessment (COA)	Any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit. Unlike biomarkers that rely completely on an automated process or algorithm, COAs depend on the implementation, interpretation, and reporting from a patient, a clinician, or an observer.
Patient-reported outcome (PRO)	A measurement based on a report that comes from the patient (ie, study participant) about the status of a patient's health condition without amendment or interpretation of the patient's report by a clinician or anyone else. A PRO can be measured by self-report or by interview, provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient (eg, pain severity or nausea) can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others.
Clinician-reported outcome (ClinRO)	A measurement based on a report that comes from a trained health care professional after observation of a patient's health condition. A ClinRO measure involves a clinical judgment or interpretation of the observable signs, behaviors, or other physical manifestations thought to be related to a disease or condition. ClinRO measures cannot directly assess symptoms that are known only to the patient (eg, pain intensity).
Observer-reported outcome (ObsRO)	A measurement based on an observation by someone other than the patient or a health professional. This may be a parent, spouse, or other nonclinical caregiver who is in a position to regularly observe and report on a specific aspect of the patient's health. An ObsRO measure does not include medical judgment or interpretation. Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life. For patients who cannot respond for themselves (eg, infants or the cognitively impaired), we encourage observer reports that include only those events or behaviors that can be observed. As an example, observers cannot validly report an infant's pain intensity (a symptom) but can report infant behavior thought to be caused by pain (eg, crying). For example, in the assessment of a child's functioning in the classroom, the teacher is the most appropriate observer. Examples of ObsROs include a parent report of a child's vomiting episodes or a report of wincing thought to be the result of pain in patients who are unable to report for themselves.
Performance outcome (PerfO)	A measurement based on a task(s) performed by a patient according to instructions that are administered by a health care professional. Performance outcomes require patient cooperation and motivation. These include measures of gait speed (eg, timed 25-foot walk test), memory recall, or other cognitive testing (eg, digit symbol substitution test).

*Source: US Food and Drug Administration (FDA), Clinical Outcome Assessment Qualification Program.

measurement may not accurately reflect the treatment-associated symptoms in this study.

Even in a trial in which the type of COA and assessment timing have been carefully considered, deviations from an assessment schedule are likely to occur. What are the consequences of these deviations? Can completion time windows provide a solution for this problem? How should we account for new adverse effects of experimental treatments that are not addressed by existing COAs? Should and could COAs be adapted according to these new and hitherto unexpected side effects?

Can Patient-reported Outcomes Be Complementary to Objective Measures of Cognitive Functioning?

COAs that have been frequently used in brain tumor research include PerfOs (cognitive function), ClinROs (Karnofsky performance status), and PROs (HRQOL and symptom burden). One of the most prominent functions in brain tumor patients relates to cognition. Neuropsychological assessments with standardized test batteries are often used to objectively assess cognitive functioning. On the other hand, cognitive functioning can also be assessed using self-ratings of impairment. Although both measures aim to identify impairments in different aspects of cognitive functioning, a strong association between the measures is lacking.[9]

The same holds true for the weak-to-moderate associations between cognitive functioning (measured using standardized test batteries and/or self-reported measures of cognitive functioning) and HRQOL,[10–12] which implies that these measures assess different concepts. Although HRQOL includes cognitive functioning, it is a multidimensional concept that also encompasses physical, psychological, and social domains as well as symptoms induced by the disease and its treatment.[13]

The available objective and subjective measures seem to be different, but could these measures be complementary in certain situations? For example, it has been suggested that PROs are less reliable once a patient has cognitive impairments, which is typical for patients with (progressive) brain tumors.[14] In such a case, an objective measure of cognition may be more appropriate as a measure of the patient's well-being. Conversely, neurocognitive assessments may be more burdensome for patients and require more time from the staff than completing a questionnaire. And, is it justified to ignore outcome measures that represent the patient's perspective?

How Do Missing Data Influence Results?

Missing data may be a major source of bias in oncology trials and particularly affect longitudinal measurements. The main reason (approximately 70%) for missing data in brain tumor trials is administrative failure (eg, questionnaires not being handed out to the patient or handed out at the wrong time).[15] Other reasons are poor health status of the patient and patient refusal.[15]

Moreover, patients who are compliant with assessments are usually those with better health status and better long-term prognosis.[15] A complete case analysis would therefore be based on a healthier subpopulation, and the results might not be representative of the entire population. Also, COAs are discontinued after disease progression in most clinical trials, which limits the evaluation of patient functioning in the subsequent course of disease.

The problem of missing data has been illustrated in a randomized controlled trial in which newly diagnosed glioblastoma patients receiving radiotherapy alone are compared with similar patients receiving radiotherapy plus concomitant and adjuvant temozolomide chemotherapy.[16] The compliance rate 4 weeks after completion of radiotherapy was higher in the patients randomized to radiotherapy (86%) than the patients randomized to combination therapy (71%).[17] A possible reason for this difference is that patients in the combination group had received more intense treatment and were therefore less able to complete HRQOL assessments. Moreover, a considerable drop in compliance rates was observed over time. At the first follow-up after treatment, only 47% and 57% of patients in the radiotherapy group and combination group, respectively, were still participating in the trial, and only 74% and 76% of these patients completed the HRQOL assessments.[17] These are likely to be patients with better health status and prognosis, and their assessments could therefore result in overestimation of the "true" HRQOL scores.

This trial clearly illustrates that missing data is a significant problem and that it may impact the results. Ideally, missing data should be avoided in order to prevent biased results. Realistically, however, this is often unpreventable. In this common situation, are there any methods that reduce the amount of missing data or are there any sophisticated statistical approaches to address this issue?

Reporting Clinical Outcome Assessment Trial Data: Statistical Significance Versus Clinical Relevance

The effectiveness of an experimental treatment is usually analyzed by statistical testing. However, some studies only report statistical differences between treatment arms, without reporting mean values[18] or the clinical meaningfulness of these differences.[18,19] In a randomized trial comparing supportive care with supportive care plus radiotherapy in elderly glioblastoma patients,[19] no statistical differences in HRQOL were found between the 2 treatment arms. Nevertheless, significant deterioration (ie, physical, cognitive and social functioning, fatigue, and motor dysfunction) was seen over time in both treatment arms. It remained unclear if these significant deteriorations were also clinically relevant deteriorations. Similarly, a prospective study that compared consecutively measured HRQOL data between newly diagnosed glioblastoma patients with and without disease recurrence found several significant differences between the 2 groups, with more negative responses from the recurrence group.[18] This study, however, only reported statistical significance without mean values for the different HRQOL scales or description of the clinical relevance for these differences. The lack of critical appraisal for the significant differences found in both studies hampered evaluation of the net clinical benefit for the treatment strategies under investigation. The 2 previous examples raise the question about how best to interpret and report COA data. Furthermore, are minimal clinically important differences available for the different COA measures to use for assessing clinical relevance of the study results?

Patient-Centered Outcome Measures in Brain Metastases: Different From Primary Brain Tumors?

Brain metastases are the most common intracranial tumors in adults.[20] The goal of treatment for patients with brain metastases, which is similar to that for patients with primary brain tumors, is to prolong survival and reduce the symptom burden to maintain or ameliorate HRQOL. Patients with brain metastases are different from those with primary brain tumors in that they have systemic cancer affecting the course of their disease besides having cancer in the brain.

Similar to clinical trials for primary brain tumors, traditional outcome measures in brain metastases trials are progression-free survival and overall survival as well as tumor response assessed by MRI. Improved survival for patients with brain metastases have resulted in increased use of COAs such as PROs and neurocognitive functioning.[21] Although brain tumor-specific HRQOL questionnaires such as the EORTC QLQ-BN20 and FACT-Br are currently used in clinical trials for patients with brain metastases,[22] these measures were originally developed for and validated in patients with primary brain tumors only.[23–25] The MDASI-BT, on the other hand, has also been evaluated for clinical utility in brain metastases.[26]

An additional concern is that systemic cancer itself, together with its treatment, may cause more general cancer symptoms such as fatigue, pain, and impairments in physical functioning. Interpretation of COA data in brain metastases trials may therefore be impacted by systemic disease. How should we deal with this? Which COAs should we use in brain metastases trials?

How to Continue

Notwithstanding these questions and observed methodological limitations, COAs have become increasingly important as outcome measures in brain tumor research. We therefore invited experts to further discuss these topics and provide guidance on use, analysis, and reporting of COAs in brain tumor research. Their papers will be published in the upcoming issues of Neuro-Oncology Practice. We thus aim to inform and educate our readers, both researchers and clinicians, about the challenges in designing, conducting, and interpreting COAs to increase the quality of COA evidence generated and facilitate its interpretation, which are essential for clinical decision-making.[27]

References

1. Patient-Centered Outcomes Research Definition 2012. Patient-Centered Outcomes Research Institute (PCORI). http://www.pcori.org/assets/PCOR-Definition-Revised-Draft-and-Responses-to-Input.pdf (Accessed December 10, 2014).
2. US Food and Drug Administration 2009. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. U.S. Department of Health and Human Services Food and Drug Administration. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf (Accessed December 10, 2014).

3. Pace A, Villani V, Zucchella C, et al. Quality of life of brain tumor patients. *European Association of NeuroOncology Magazine*. 2012;2: 118–122.
4. Dirven L, Reijneveld JC, Taphoorn MJ. Health-related quality of life or quantity of life: a difficult trade-off in primary brain tumors? *Semin Oncol*. 2014;41:541–552.
5. Osoba D. Rationale for the timing of health-related quality-of-life (HQL) assessments in oncological palliative therapy. *Cancer Treat Rev*. 1996;22: Suppl A: 69–73.
6. Osoba D. What has been learned from measuring health-related quality of life in clinical oncology. *Eur J Cancer*. 1999;35:1565–1570.
7. van den Bent MJ, Carpentier AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. *J Clin Oncol*. 2006;24:2715–2722.
8. Taphoorn MJ, van den Bent MJ, Mauer ME, et al. Health-related quality of life in patients treated for anaplastic oligodendroglioma with adjuvant chemotherapy: results of a European Organisation for Research and Treatment of Cancer randomized clinical trial. *J Clin Oncol*. 2007;25:5723–5730.
9. Biglia N, Bounous VE, Malabaila A, et al. Objective and self-reported cognitive dysfunction in breast cancer women treated with chemotherapy: a prospective study. *Eur J Cancer Care (Engl)*. 2012; 21:485–492.
10. Aaronson NK, Taphoorn MJ, Heimans JJ, et al. Compromised health-related quality of life in patients with low-grade glioma. *J Clin Oncol*. 2011;29:4430–4435.
11. Boele FW, Zant M, Heine ECE, et al. The association between cognitive functioning and health-related quality of life in low-grade glioma patients. *Neurooncol Pract*. 2014;1:40–46.
12. Klein M, Taphoorn MJ, Heimans JJ, et al. Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. *J Clin Oncol*. 2001;19:4037–4047.
13. Aaronson NK. Quality of life: what is it? How should it be measured? *Oncology (Williston Park)*. 1988;2:69–76, 64.
14. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol*. 2004;3:159–168.
15. Walker M, Brown J, Brown K, et al. Practical problems with the collection and interpretation of serial quality of life assessments in patients with malignant glioma. *J Neurooncol*. 2003;63:179–186.
16. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987–996.
17. Taphoorn MJ, Stupp R, Coens C, et al. Health-related quality of life in patients with glioblastoma: a randomised controlled trial. *Lancet Oncol*. 2005;6:937–944.
18. Shields LB, Choucair A, Choucair AK. Quality of life measures as a preliminary clinical indicator in patients with primary brain tumors. *Surg Neurol Int*. 2013;4:48.
19. Keime-Guibert F, Chinot O, Taillandier L, et al. Radiotherapy for glioblastoma in the elderly. *N Engl J Med*. 2007;356: 1527–1535.
20. Patchell RA. The management of brain metastases. *Cancer Treat Rev*. 2003;29:533–540.
21. Witgert ME, Meyers CA. Neurocognitive and quality of life measures in patients with metastatic brain disease. *Neurosurg Clin N Am*. 2011; 22:79–85, vii.
22. Chiu L, Chiu N, Zeng L, et al. Quality of life in patients with primary and metastatic brain cancer as reported in the literature using the EORTC QLQ-BN20 and QLQ-C30. *Expert Rev Pharmacoecon Outcomes Res*. 2012;12:831–837.
23. Osoba D, Aaronson NK, Muller M, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Qual Life Res*. 1996;5:139–150.
24. Taphoorn MJ, Claassens L, Aaronson NK, et al. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. *Eur J Cancer*. 2010;46: 1033–1040.
25. Weitzner MA, Meyers CA, Gelke CK, et al. The Functional Assessment of Cancer Therapy (FACT) scale. Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. *Cancer*. 1995;75:1151–1161.
26. Armstrong TS, Gning I, Mendoza TR, et al. Clinical utility of the MDASI-BT in patients with brain metastases. *J Pain Symptom Manage*. 2009;37:331–340.
27. Dirven L, Taphoorn MJ, Reijneveld JC, et al. The level of patient-reported outcome reporting in randomised controlled trials of brain tumour patients: a systematic review. *Eur J Cancer*. 2014;50: 2432–2448.