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Review

Health related quality of life assessment methodology and reported outcomes in randomised controlled trials of primary brain cancer patients

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Abstract

Over the last 20 years, the assessment of quality of life (QOL) has become an important endpoint in cancer clinical trials, helping us to understand patient survival and QOL experiences and aiding clinicians in providing the best possible treatment and care, with the least toxicity and ill-effects. In primary brain cancer, these are critical issues. Survival is often limited and treatment difficult to tolerate. In recent years, some authors have questioned the methodological quality of the investigations and the reporting of QOL assessments from randomised controlled trials (RCTs), of cancer patients yet this assessment has never specifically focused on brain cancer. This paper therefore reports a systematic review of the research methodology and QOL assessment reporting in brain cancer patients in RCTs. The search was mainly performed on the following databases: Medline, Cancerlit and the Cochrane Controlled Trials Register. We identified only five RCTs, enrolling a total of 1026 patients. In many of these studies, we had identified methodological limitations which would hinder the interpretation of the results. These included a lack of detailed reporting regarding missing data, use of poorly validated tools, and general limitations regarding the presentation and interpretation of the results. Based on the results of our review, we make recommendations for future investigations to avoid these shortcomings.

Keywords: Brain cancer; Quality of life; Randomised controlled trials; Systematic review

1. Introduction

Unlike secondary brain tumours, primary brain tumours begin directly in the brain tissue. This relatively infrequent disease affects approximately 2% of all adult cancer sufferers [1]. Brain cancer can be difficult to diagnose and is invariably challenging to treat. Treatment options vary widely. Certain primary brain tumours can be treated by surgery alone, others by surgery and radiation or combination therapy, surgery, radiation therapy and chemotherapy. Brain tumours requiring the combination of all three treatments are usually incurable [2].

The most common brain tumour, glioma, accounts for over 50% of all primary central nervous system tumours [3]. There are several types of gliomas, including non-infiltrating and infiltrating astrocytic, ependymal, oligodendroglial and mixed tumours [4]. Malignant gliomas are classified on the grounds of the tumour-cell type and vary from low-grade to high-grade malignant gliomas such as anaplastic astrocytoma (AA) or astrocytoma grade III, and glioblastoma multiforme (GBM) or astrocytoma grade IV [5]. Most malignant gliomas are AA and GBM [6]. High-grade gliomas (grades III and IV) comprise the majority (80–85%) of all primary brain tumours [7]. Astrocytoma grades I and II are considered low-grade malignant gliomas and account for approximately 20% of all gliomas [5]. However, most low-grade gliomas are grade II, as grade I gliomas are extremely unusual [8]. Following primary treatment, most patients will have recurrences of the tumour and subsequent treatment options are limited and palliative [6]. For high-grade gliomas, there is no successful treatment; patients can suffer from a wide range of symptoms

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that profoundly effect quality of life (QOL). The median survival rate of patients with glioblastoma is less than a year from diagnosis, whereas the median survival rate for AA patients is approximately 18 months [1]. Given the extremely poor prognoses for malignant gliomas [6], and a lack of effective therapies for significant survival improvements [9–12], QOL aspects should be seen as a critical issue in the treatment of brain cancer.

Patients with brain tumours may suffer from a range of major health-impairing problems reducing QOL: cognitive dysfunction and personality changes related to the tumour-invaded area of the brain, while invasive and/or aggressive therapy may compromise the functioning of normal brain tissue.

The side-effects of cancer treatment often include weakness, fatigue, coordination problems, difficulty in speaking and thinking and hair loss [7]. Hence, aspects of treatment-related QOL should be of primary importance when comparing new or different medical therapies in clinical trial results.

However, while QOL is regarded as important, recent work suggests many previous randomised control trial (RCT) publications about cancer are limited in both design and reporting [13]. Such criticism has raised concerns with some authors regarding, in general, the validity of findings from RCTs with QOL assessments. However, to date, no detailed systematic methodological review of the quality of the conduct and reporting of QOL results from RCTs for brain cancer patients has appeared.

Therefore, this paper aims to provide a systematic review of all clinical trials involving QOL issues in order to evaluate assessment methodology and report on the impact of new treatments on patients QOL. In order to do this, and to retrieve the highest level of scientific evidence, the search was restricted to the published RCTs.

2. Review methodology

2.1. Search strategy for identification of studies

A literature search was undertaken on the following databases: Medline (1980–2001), Cancerlit (1980–2001), the Cochrane Controlled Trials Register (Cochrane Library 2000, Issue 3) and the online National Cancer Institute database for clinical trials. In order to retrieve all of the relevant studies, significant articles occurring as references in the literature were also included. Finally, for a more comprehensive search on Medline, Cancerlit and at the Cochrane Library, additional keywords related to QOL were included: *visual disorder*, *communication deficit*, *motor dysfunction*, *pain* and *fatigue*. Keywords for the searching strategy included *brain cancer*, *brain tumors*, *glial tumors*, *nonglial tumors*, *glioblastoma*, *malignant glioma*. As for Medline and Cancerlit searches, in order to retrieve all the clinical trial studies, regardless of their type and the phase, the search was restricted using the subheading *clinical trial* as the publication type. No restriction was placed on the search-field description or on the language of the article. As for the online National Cancer Institute database for clinical trials, the following limits were used: type of cancer (adult brain tumours); phase of trial (phase III); status of trial (closed trial). No restrictions were performed on the type of trial, trial location, stage of cancer, treatment modalities and sponsor of trial. Just this latter search yielded 59 trials whose endpoints were reviewed.

3. Criteria for considering studies for this review

3.1. Types of participants

Participants were confined to adult patients (aged 18 years and over) with a primary brain tumour, or those with any recurrence, regardless of the type and grade of the tumour. Patients with brain metastases arising from other cancer sites, or with a single brain metastases from an extracranial primary cancer, are excluded from this review.

3.2. Types of intervention

This study included any medical intervention including conventional and ablative endocrine surgery, chemo-, radio-, endocrine, gene, hormone and interleukin therapies. Because this paper is aimed at evaluating studies dealing with the effects of new medical treatments on patient's QOL, studies dealing with either psychological intervention or non-medical intervention(s) were not taken into account.

3.3. Types of outcome measures examined

As QOL was the main outcome measure sought, any studies including QOL either as a primary or secondary endpoint were considered. However, only patient's self-reported measures of QOL are taken into account. Therefore, studies including exclusively physician-assessed QOL measures (such as *Karnofsky's Performance Status Index*) were excluded. This rationale is supported by evidence showing considerable variability in QOL results between doctor-assessed and cancer patient self-assessed outcomes [14], and by a generalised consensus that patients are the best primary source of information about their individual QOL [15].

3.4. Types of studies

Studies included for review had to be randomised-controlled clinical trials, phases II and III (including

prospective randomised studies), comparing different medical treatments with not less than 30 patients in each study and published between 1981 and 2001. Phase I studies were not taken into consideration. Randomized trials, where the method of randomization was not specified, were also included. The search was restricted to the RCTs because they represent the *gold standard* by which healthcare professionals make decisions about treatment effectiveness.

4. Methods of evaluation of the QOL studies

Two reviewers analysed the identified RCTs independently. When disagreement about the analysis of a study was encountered, the authors revisited the original article to reconcile any difference of opinion. At the present time, no *gold standard* exists against which QOL assessment methodology in cancer clinical trials can be measured. Therefore, the authors based their evaluation of the available literature on the principle of *good practice* in reporting QOL [15,16]. This methodology was previously reported [17]. Four main categories were identified as shown in Tables 1–4: demographics, trial design, QOL assessment methodology, and methods of analysis and results.

With QOL issues, attention was paid mainly to the instrument type, rationale for the instrument use, covered domains for a brain cancer population, presentation of psychometric details reported (especially where the instrument used was not well known in the literature), and the cross-cultural validity of the instrument.

5. Results

5.1. Description of studies

The five studies selected are reviewed according to the four clusters provided in Tables 1–4 where data are summarized.

5.2. Demographics and trial design

All five studies are published in English. Two studies were undertaken in an international context [10,18] and three in a national context [11,19,20]. While four trials were published during 1991–2001, only one [20] was published between 1981 and 1991. Evidence of industry funding was found in only one trial [18].

Some variation in the disease grade of the enrolled patients is evident. Three studies [11,18,19] enrolled exclusively high-stage patients (grades III and IV); Trojanowski and colleagues [20] used mixed grades, and Kiebert and colleagues [10] enrolled only low-grade glioma patients. None of the studies had QOL as a primary endpoint, although some of them [10,18,19] address it in a comprehensive way. Trojanowski and colleagues [20] also addressed QOL issues in a comprehensive way, but limiting the discussion to neuropsychological functions without taking into consideration some other relevant aspects (e.g. social and emotional well-being).

As for the medical treatment modalities, radiation therapy intervention was predominant. Bampoe and colleagues [19] compared conventional external radiation therapy, used alone, with conventional radiation therapy plus a brachytherapy boost. Trojanowski and colleagues [20] compared the effectiveness of postoperative radiotherapy alone versus radiotherapy combined with chemotherapy. Pickles and colleagues [11] compared pion therapy versus conventional therapy irradiation. Kiebert and colleagues [10], randomised low-grade glioma patients to receive either low-dose (45Gy) or high-dose (59.4 Gy) radiotherapy with conventional techniques. Yung and colleagues [18] evaluated two different chemotherapy treatments—temozolomide vs. procarbazine.

Trojanowski and colleagues [20] and Yung and colleagues [18] do not report the method of randomisation. In the European Organisation for Research and Treatment of Cancer (EORTC) trial (22844), conducted by Kiebert and colleagues [10], the method of randomisation was carried out at EORTC Data Center in Brussels,

Table 1
Demographics

Authors [Ref.]	Language of article	Journal	Year of publication	Study location[a]	Industry funded[b]
Trojanowski and colleagues [20]	English	*Journal of Neurosurgery*	1989	Poland	No
Pickles and colleagues[11]	English	*International Journal of Radiation Oncology, Biology, Physics*	1997	Canada	No
Kiebert and colleagues[10]	English	*European Journal of Cancer*	1998	Europe	No
Bampoe and colleagues[19]	English	*Journal of Neurosurgery*	2000	Canada	No
Yung and colleagues[18]	English	*British Journal of Cancer*	2000	International	Yes

[a] Assessed as "International" if the trial involved patients from different continents.
[b] Assessed if explicitly stated or if authors were related to a pharmaceutical company.

Table 2
Trial design

Authors [Ref.]	Method of randomisation stated	Informed consent reported	Trial inclusion and exclusion criteria reported	Overall number of patients enrolled	Sex	Disease stage/ diagnosis	Type of intervention	QOL endpoints. primary/ secondary	QOL compliance mandatory	Hypothesis stated
Trojanowski and colleagues [20]	No	No	Yes	198	Mixed	Low and high-grade glioma	Postoperative radiotherapy combined with CCNU chemotherapy versus radiotherapy alone	Secondary	No	No
Pickles and colleagues [11]	Yes	Yes	Yes	84	Not reported	Grades III and IV glioma	Pion therapy versus conventional photon irradiation	Secondary	No	No
Kiebert and colleagues [10]	Reported in Karim and colleagues [21]	Yes	Reported in Karim and colleagues [21]	379	Mixed	Grades I and II	High dose (59.4 Gy in 6.5 weeks) versus low dose (45 Gy in 5 weeks) of radiotherapy with conventional techniques	Secondary	No	No
Bampoe and colleagues [19]	Reported in Laperriere and colleagues [9]	No	Yes	140	Not reported	Malignant astrocytomas	Conventional external radiation therapy alone versus conventional radiation therapy plus a brachitherapy boost	Secondary	No	No
Yung and colleagues [18]	No	Yes	Yes	225	Mixed	Glioblastoma multiforme	Temozolomide versus Procarbazine	Secondary	No	Reported in Osoba and colleagues [25]

Table 3
Quality of life assessment methodology

Authors [Ref]	QOL Instrument used	QOL baseline compliance reported	Validity data presented	Reliability data presented	Cultural validity of translation verified[a]	Rationale for instruments	Adequacy of QOL domains covered	Instrument administration reported	Describe timing of assessments
Trojanowski and colleagues [20]	Neuropsychological test battery	Yes (62%)	No	No	N/A	Yes	Limited	No	Yes
Pickles and colleagues [11]	University of Toronto instrument	Yes (62%)	Limited	Reported in Bampoe and colleagues[19]	N/A	No	Yes	No	Yes
Kiebert and colleagues [10]	A 47 item QOL adapted tool, from different questionnaires	Yes (22%)	No	Yes	Not reported	Yes	Yes	No	Yes
Bampoe and colleagues [19]	University of Toronto instrument	Yes (66%)	Limited	Yes	N/A	Yes	Yes	No	Yes
Yung and colleagues [18]	EORTC QLQ C30/B20	Yes (81.4%)	Yes	Yes	Yes	Yes	Yes	No	Yes

EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life questionnaire; QOL, quality of life.
[a] Assessed as N/A if the instrument was validated in the same country where the trial was carried out.

Table 4
Methods of analysis and results

Authors	Test of statistical significance for QOL between arms	QOL difference between treatment arms	Clinical significance addressed	Overall presentation of results	Missing data documented
Trojanowski and colleagues [20]	Yes	No	No	Yes	No
Pickles and colleagues [11]	No	N/A	No	Limited	No
Kiebert and colleagues [10]	Yes	Yes	No	Yes	Yes
Bampoe and colleagues [19]	Yes	No	Yes	Yes	Yes
Yung and colleagues [18]	Reported in Osoba and colleagues [25]	Reported in Osoba and colleagues [25]	Reported in Osoba and colleagues [25]	Reported in Osoba and colleagues [25]	Reported in Osoba and colleagues [25]

and organised with stratification for each institute; detailed data are reported in Karim and colleagues [21]. The randomization process for the study carried out by Bampoe and colleagues [19] was reported elsewhere [9]. All the studies reported information on patient eligibility criteria.

5.3. QOL measurement evaluation

Among the studies reviewed, there is no agreement on the QOL assessment methodology and, generally, poor details about the timing of assessments and instrument administration. Trojanowski and colleagues [20] used a neuropsychological test battery, a set of 28 easy-to-perform tasks, evaluating areas related to brain cancer patient's QOL, including speech, memory, praxis, sensory and visual recognition. Execution of each test was given, non-linearly, a value relating it to the degree of single-function disturbance. The scores were calculated using coefficients weighted according to the importance of various higher brain functions for QOL. The coefficients were higher for more important functions and lower for those of lesser importance. These scales were calculated using a panel of expert neuropsychologists. A sum of scores for test execution multiplied by the coefficient for each test divided by the sum of the coefficients yielded an overall score representing the status of brain functioning identified by authors as the 'neuropsychological life-quality coefficient'. Although this trial assessed neuropsychological aspects specifically related to important aspects of brain cancer patient's QOL, it does not provide information on other core QOL domains relevant for cancer patients such as social and emotional well-being [22]. No data about the psychometric features of the tool, validity, reliability and responsiveness are provided. It is important to note that at the time of this study, no robust QOL measures suitable for brain cancer patients were available. The authors collected QOL data pre-surgery and at 6, 12 and 24 months postsurgery.

Two trials used the same instruments, namely, the University of Toronto Scale, a tool covering the main areas of brain cancer patient's QOL. In the Pickles and colleagues [11] study, very limited details are reported about the structure of the tool and the related psychometric features. A rationale for the selection of the instrument is not given, although QOL information regarding the timing of assessments is provided.

Bampoe and colleagues [19] also used the University of Toronto instrument reporting full details on the QOL assessment methodology and the features of the QOL tool. The instrument consists of a 16-item core dealing with general aspects relating to cancer patient's QOL such as physical, emotional and social well-being together with a 13-item brain tumour module. The core was derived from another QOL measure, the *Sickness Impact Profile* [23]. The brain tumour module is focused on assessing specific dimensions such as headache, memory and concentration. All items are presented on a linear-analogue scale. Reliability data are reported as for Cronbach's alpha-coefficient and test–retest reliability. However, while data for validity are limited, rationale for instrument usage is provided along with the timing of assessment. QOL data are carefully reported at baseline and thereafter at 3-monthly intervals.

Kiebert and colleagues [10] provide a detailed rationale for the QOL instrument employed with the questionnaire fully reported. The researchers used an *ad hoc* QOL measure adapted from a variety of sources including the *Sickness Impact Profile*, the *Rand Corporation Health Insurance Study battery questionnaires*, the *Center for Epidemiological Studies Depression Scale*, and items from EORTC questionnaires. This compilation resulted in a 47-item questionnaire adequately covering the main QOL dimensions related to brain cancer patients including social, psychological, physical and other specific symptoms; memory and concentration, sensory deficits and headaches. Reliability data, assessed by Cronbach's alpha-coefficient, were reported. Among the 27 institutions participating in the trial, 14 contributed with QOL data. Although different European countries were involved, instrument cultural validity is not reported. The schedule of QOL assessment occurred at baseline, at 3, 6 and 12 months after radiotherapy, and annually thereafter.

Yung and colleagues [18] used the EORTC QLQ-C30 (+3), plus the EORTC brain module (EORTC BN-20). This instrument has proven psychometric features that adequately cover all QOL aspects related to the brain cancer patients. It provides a general evaluation for such outcomes as role, social and physical functioning, and a set of items assessing specific health-related QOL problems: visual disorders, communication deficit and motor dysfunction [24]. Rationale for instrument usage and QOL baseline data are provided, as well as information on the QOL assessment timing. Details on the method of administration are not reported. Osoba and colleagues [25] reported, in a separate publication, a detailed analysis of the QOL assessment.

5.4. Methods of analysis and results

Test of statistical significance for QOL data per arm was applied in four studies [10,18–20], but just one of them showed major significant differences between the two treatment arms in several important domains [18].

Kiebert and colleagues [10] report result details showing that patients who received high-dose radiotherapy reported significantly more *fatigue/malaise* and *insomnia* immediately after radiotherapy, and were more impaired in *leisure time activities* and experienced poorer *emotional functioning* at 7–15 months post-randomisation follow-up. The remaining QOL domains showed no significant differences statistically. The study revealed no clinical benefit in terms of overall survival and progression-free survival. The Trojanowski and colleagues [20] study shows no significant differences between the median survival time for patients treated with additional radiotherapy and patients receiving additional chemotherapy. Although limited to neuropsychological aspects, no significant QOL difference, statistical, was found between the two treatment arms. Bampoe and colleagues [19] did not find a QOL statistical difference between patients who only received conventional external radiation therapy and patients who received additional brachytherapy boost. Clinical significance and presentation of results are reported in detail. In the study carried out by Yung and colleagues [18], temozolomide is shown to significantly improve progression-free survival at 6 months. A comprehensive QOL analysis of this trial was published by Osoba and colleagues [25] showing improvements from baseline in the scores of seven preselected QOL domains (role and social functioning, global quality of life, visual disorders, motor dysfunction, communication deficit and drowsiness) for patients treated with temozolomide who were progression-free at 6 months. The Pickles and colleagues [11] study shows no differences in terms of survival or time to local recurrence. As for QOL analysis, no test of statistical significance was applied, and therefore any evidence of QOL differences between the two groups was not detectable. The clinical significance of QOL results is not addressed and the presentation of results in general is limited.

6. Conclusion

Using the predetermined selection and eligibility criteria, only five RCTs were found. In general, there is a paucity of studies addressing QOL as a part of the trial design. Although some studies reviewed met the criteria for the number of patients and trial design, they did not assess QOL by means of patient self-reported measures [26–30]. The use of non-patient-based QOL assessments (e.g. *Karnofsky performance measure*) are known to be poor estimates of patient's QOL, and are therefore of limited value in providing an accurate assessment of a patient's QOL. This is also supported from evidence showing a considerable variability in the results reported between doctor and cancer patient's QOL outcomes [14,31,32]. Furthermore, there is a generalised consensus that patients are the primary source of information on their particular QOL making patient self-reported measures desirable in clinical trials [15,33]. Patient-based QOL questionnaire administration offers the most direct means of evaluating the subjective morbidity associated with the disease and its treatment. Empirical evidences with cancer patients have shown that physician's ratings may not reflect accurately the functional health and symptom experience of their patients [34].

The selected studies used different QOL assessment methodologies making the results difficult to compare. It is surprising that just one trial showed major significant differences in QOL outcomes [18]. Possibly, differences in some of the trials may have been hampered due to the limitations identified and reported above. With the exception of some studies [10,18,19], these limitations include limited reporting of the QOL assessment results. This is apart from the failure to have a clear hypothesis before the commencement of the trial, as well as little attention being paid to the clinical significance of the results. Although no international *gold standard* guidelines exist for assessing QOL in clinical trials, there is an urgent need to improve the methodology and standardise the procedures in order to compare patient's QOL outcomes. Apart from the Yung and colleagues [18] study, which shows some significant clinical results in terms of survival, the other studies reviewed did not show any significant clinical changes and failed to affect survival when compared with standard therapy.

While this review has attempted to undertake a systematic review of all the available published literature, one possible limitation is that not all RCTs comprising QOL components were identified. However, opinions of

some experts in brain cancer research were fielded to try to ensure selected studies meet the stated criteria. Despite these potential limitations, this paper has two key findings: QOL is being neglected as an endpoint in cancer clinical trials with brain cancer patients. This paper suggests this has occurred frequently over the last two decades. QOL data can be invaluable for caring and developing new treatments for brain cancer patients. The authors urge a more comprehensive assessment of treatment effects be given consideration when investigating the brain cancer patient's QOL. Furthermore, there is a need to improve the conduct and reporting of the RCTs in QOL studies of brain cancer patients. Many of the limitations noted may be related to historical difficulties the investigators faced including the limited availability of robust QOL tools, and a limited understanding of the requirements for reporting QOL studies. However, there are now a number of publications that suggest minimum standards for reporting QOL studies [15,16]. It cannot be discounted that certain aspects of the reviewed studies were not available because of limitations imposed by journal space and/or editorial constraints. However, these constraints are unlikely to lead to the exclusion of critical factors such as statements of hypothesis, and justification for selection measures. In many respects, the authors' expectation is the hope that, as the science of QOL develops and becomes more acceptable, investigators will consider giving greater attention to the design of and reporting on QOL studies in brain cancer patients.

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