Support Care Cancer (2015) 23:2731–2737
DOI 10.1007/s00520-015-2637-5

ORIGINAL ARTICLE

Minimal clinically important differences in the EORTC QLQ-BN20 in patients with brain metastases

Erin Wong · Liying Zhang · Marc Kerba · Palmira Foro Arnalot · Brita Danielson · May Tsao · Gillian Bedard · Nemica Thavarajah · Paul Cheon · Cyril Danjoux · Natalie Pulenzas · Edward Chow

Received: 30 July 2014 / Accepted: 26 January 2015 / Published online: 10 February 2015
© Springer-Verlag Berlin Heidelberg 2015

Abstract
Introduction Quality of life (QOL) is an important treatment endpoint in advanced cancer patients with brain metastases. In clinical trials, statistically significant changes can be reached in a large enough population; however, these changes may not be clinically relevant.
Objective The objective of this study was to determine the minimal clinically important difference (MCID) for the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire brain module (EORTC QLQ-BN20) in patients with brain metastases.
Methods Patients undergoing radiotherapy for brain metastases completed the EORTC QLQ-BN20 and QLQ-C30/C15-PAL at baseline and 1-month follow-up. MCIDs were calculated for both improvement and deterioration using anchor- and distribution-based approaches. The anchor of overall QOL (as assessed by question 30 or question 15 on the QLQ-C30 and QLQ-C15-PAL, respectively) was used to determine meaningful change.
Results A total of 99 patients were included. The average age was 61 years, and the most common primary cancer sites were the lung and breast. Statistically significant meaningful differences were seen on two scales. A decrease of 6.1 (95 % confidence interval (CI) 0.8 to 11.4) units and 13.8 (0.2 to 27.4) units was required to represent clinically relevant deterioration of seizures and weakness of legs, respectively. Distribution-based MCID estimates tended to be closer to 0.5 SD on the EORTC QLQ-BN20.
Conclusion Understanding MCIDs allows physicians to determine the impact of treatment on patients' QOL and allows for determination of sample sizes for clinical trials. Future studies should be conducted to validate our findings in a larger population of patients with brain metastases.

Keywords Brain metastases · Meaningful change · Quality of life

E. Wong · L. Zhang · M. Tsao · G. Bedard · N. Thavarajah · P. Cheon · C. Danjoux · N. Pulenzas · E. Chow (✉)
Rapid Response Radiotherapy Program, Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Toronto, ON, Canada M4N 3M5
e-mail: Edward.Chow@sunnybrook.ca

M. Kerba
Department of Radiation Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada

P. Foro Arnalot
Parc de Salut Mar Hospital de l'Esperança, Barcelona, Spain

B. Danielson
Department of Radiation Oncology, Cross Cancer Institute, Edmonton, AB, Canada

Introduction

Approximately 20–40 % of cancer patients will eventually develop brain metastases [1]. It is the most common type of brain neoplasms in comparison to primary brain cancers. The most common primary cancer sites to metastasize to the brain are the breast, colorectal, lung, melanoma, and kidney [1]. Brain metastases are associated with a multitude of symptoms such as, but not limited to, headaches, motor weakness, balance problems, altered mental status, visual problems and seizures, with headaches and focal weakness being the most common symptoms [2–4].

Age, performance status (PS), extent of brain metastases and extracranial diseases ultimately aid in the decision-making process in determining the choice of treatment for patients with brain metastases [5]. The standard of care for multiple brain metastases is to offer whole brain radiotherapy (WBRT) and dexamethasone [2]. For solitary brain

metastasis, in patients with good PS, brain metastases may be treated with surgical resection or with stereotactic radiotherapy [5]. In certain instances, such as in patients with poorer PS, supportive care such as symptom management with medication only may be offered [2]. Chemotherapy is not commonly considered as a treatment option for patients with brain metastases due to the complexity of the blood-brain barrier, which limits the entry of the treatment to the brain or limits its concentration in the blood to the brain [6].

Despite multiple treatment options, patients stricken with brain metastases have limited survival with an observed medial survival of 3–6 months following WBRT. Improved survival has been observed in patients treated with radiosurgery or surgical resection [5]. Due to limited survival, the improvement of health-related quality of life (HRQOL) through palliation of symptoms takes priority [7].

To assess the impact of brain metastases on HRQOL, tools have been employed [7]. One such tool is the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire brain module (EORTC QLQ-BN20) in conjunction with the EORTC QLQ-C30, the general questionnaire [8].

Determining the minimal clinically important difference (MCID) in quality of life (QOL) instruments is important for healthcare practitioners and researchers alike. MCID is the smallest difference in score which is clinically important [9, 10]. Currently, clinical trials determine effectiveness of treatments on HRQOL through establishing statistical significance. However, statistical significance may not reflect a clinically relevant change, as statistical significance can be reached in a large enough sample size [11, 12]. The objective of this study was to determine the MCIDs in the EORTC QLQ-BN20 in patients with brain metastases.

Methods

Patient population

This analysis included pooled data from two prospective data sets. From October 2009 to July 2010, patients with brain metastases referred for WBRT from four Canadian centres and one Spanish centre were included in this study. All research was conducted upon approval by the respective research ethics board at each institution. Patients with brain metastases referred for WBRT, radiosurgery/gamma knife or neurosurgical resection were approached for the study. Patients over the age of 18 years with histologically or radiologically documented brain metastases were included.

Data collection

At baseline consultation, patients completed the EORTC QLQ-BN20 and either the EORTC QLQ-C30 or the EORTC QLQ-C15 PAL. Demographic information was also collected. This included age, gender, primary cancer site, Karnofsky performance status (KPS), cancer and radiation treatments. Patients also completed the BN20 and C30/C15-PAL at 1-month follow-up.

European Organization for Research and Treatment of Cancer—brain module (EORTC QLQ-BN20) instrument and scoring

The EORTC QLQ-BN20 is the brain cancer supplementary module to the EORTC QLQ-C30, the general "core" questionnaire. It contains 20 items, broken into four multi-item scales (13 items) and 7 singular items. The four subscales of the BN20 are future uncertainty (4 items), visual disorder (3 items), communication deficit (3 items), and motor dysfunction (3 items). The remaining 7 items assess symptoms of disease such as headaches, seizures, drowsiness, weakness of legs, bladder control and treatment toxic effects such as hair loss and itchy skin. Each item is rated on a Likert scale from 1 to 4 (1='not at all', 2='a little', 3='quite a bit', and 4='very much'). All items were scored based on EORTC scoring procedure. Raw scores were standardized using linear transformation so that scores ranged from 0 to 100. For all four scales and 7 single items, a higher score represents poorer QOL.

Statistical analysis

Descriptive analysis was summarized as mean, standard deviation (SD), median, range for age and KPS and as proportions for categorical variables such as gender, primary cancer site, etc.

The methodology described by Maringwa et al. was used to determine MCIDs in the EORTC QLQ-BN20. This has been applied to other EORTC QOL tools [11, 13]. There are two different methods for determining MCIDs: anchor-based and distribution-based. Both anchor- and distribution-based approaches were utilized in the determination of MCID in the EORTC QLQ-BN20.

In the anchor-based approach, an "anchor" or external criterion is used. There are certain requirements for the selection of anchor: independently interpretable, clinically relevant, definable and moderately correlated with the instrument. Ultimately, for the anchor to be effective, it must be associated with HRQOL as determined by a moderate correlation ($r > 0.30$) and relevance to the disease [14]. Commonly used anchors are PS or progression of disease. The anchor is used to determine meaningful change. For our current analysis, patient-reported overall QOL as rated by the question: "How would you rate your overall quality of life during the past week?" (scale 1–7; the higher the scale, the better overall QOL) as taken from the EORTC QLQ-C30 or C15-PAL was used as the clinical marker to which the MCID was calculated.

Mean scores and mean change scores for all EORTC QLQ-BN20 scales and single items and overall QOL were calculated for each patient. As only four and nine patients had two units of increase and decrease from baseline, respectively, and three and six patients had more than two units of increase and decrease from baseline, respectively, one-unit change was considered as the overall QOL anchor. Patients with greater than one unit change in overall QOL were excluded from the MCID calculation as these changes were considered to be greater than minimal changes. Changes in overall QOL were categorized into three groups: deteriorated by one unit, no change and improved by one unit. Each individual patient's QLQ-BN20 change scores were assigned to one of the three "clinically meaningful" categories as defined by the overall QOL anchor. To control for the amount of change in QLQ-BN20 that occurred to patients who did not change according to the overall QOL, MCID and its 95 % confidence interval (CI) were estimated by calculating the difference in the mean scale change between adjacent categories (e.g. 'improved' vs. 'no change' and 'no change' vs. 'deteriorated'). MCIDs were determined to be statistically significant if the 95 % CI did not include zero.

Spearman correlation analysis was conducted between the overall QOL item from the accompanying C30 or C15-PAL and the BN20 scores at baseline and follow-up, respectively. Clinical relevance of the BN20 scale to overall QOL scale is represented by moderate correlation between QOL and BN20 scales and singular items which is represented by $|r \geq 0.3|$.

The distribution-based approach is based on the idea that MCIDs can be estimated based on the distribution of scores within a sample of patients. As such, distribution-based approach is calculated by determining the standard deviations of scores and change scores and also the standard error of measurement (SEM). The SEM measures the precision of the EORTC QLQ-BN20 or other HRQOL instruments [15]. Standard deviations of scores and change scores were divided by fractions. In this current analyses, 0.2 SD, 0.3 SD, 0.5 SD and SEM (estimated by $SD \times \sqrt{1-\text{reliability coefficient}}$, describing the error associated with the measure) for the QLQ-BN20 were calculated and considered to be MCID estimates. All analyses were conducted using Statistical Analysis software (SAS version 9.3 for Windows; SAS Institute Inc., Cary, NC, USA).

Results

A total of 99 patients who completed both the baseline and follow-up BN20 and C30 or C15-PAL were included for analysis (Table 1). Patient's age ranged from 22 to 83 years with an average of 61±11.0 years. KPS of patients ranged from 40 to 100, with a median of 80. Of the included patients, 56 (57 %) were females. The most common primary cancer sites were the lung (54 %) and breast (22 %). Most patients received radiation, either radiosurgery/gamma knife (36 %) or WBRT (57 %). The remainder of patients received neurosurgery (6 %), and one patient received symptom management treatment (1 %). Most patients were outpatients (96 %). Our study had patients with one brain metastasis (33 %), two to three brain metastases (37 %) and multiple (more than three) brain metastases (30 %).

Of the four EORTC QLQ-BN20 subscales at baseline, future uncertainty ($r=-0.45$) and motor dysfunction ($r=-0.31$) had moderate or better correlation with the anchor. While of the seven symptoms and treatment toxicity, only headache ($r=-0.31$) had a Spearman correlation of at least 0.30 with the overall QOL anchor. At follow-up, of the four EORTC QLQ-BN20 subscales, only future uncertainty domain ($r=-0.48$) had significant correlation with overall QOL anchor. There was a lower correlation ($r<|0.30|$) between any BN20 scale changes and overall QOL anchor changes (Table 2).

All four subscales and seven symptoms and treatment toxicities on the EORTC QLQ-BN20 were included in the MCID calculation. At follow-up, there were 36 patients with no overall QOL change, 21 patients with overall QOL increase by one unit from baseline (improved) and 20 patients with one-unit decrease from baseline at 1 month follow-up (deteriorated). The mean scores for all EORTC QLQ-BN20 scales and single items for patients improved by one unit in overall QOL, no change in overall QOL and deteriorated by one unit in overall QOL are shown in Table 3. The mean change scores between adjacent anchor-based groups are shown in Table 3. For improvement, the mean change scores represented the difference between the improvement and no-change group. For deterioration, the mean change scores represented the difference between the deterioration and no-change group.

MCID for improvement and no change groups did not demonstrate statistical significance for the four subscales and seven symptoms or treatment toxicity. However, for deterioration, two of the seven symptoms and treatment toxicity demonstrated statistically significant MCID. A change of 6.1 (95 % CI, 0.8 to 11.4) units in seizures and 13.8 (95 % CI, 0.2 to 27.4) units in weakness of legs, respectively, were required to establish clinical significance (Table 3). When compared to anchor-based MCID estimates, the distribution-based MCID estimates of 0.5 SD were the closest in comparison (Table 4).

Discussion

Since 1990, a shift in clinical trial endpoints has occurred [16]. Previously, clinical trial endpoints have mainly consisted of concrete endpoints that are patient-independent such as radiological or physical changes/progression or survival/progression-free survival. However, patient-reported outcomes such as QOL have gained importance and become more widely incorporated into clinical trials as exemplified

Table 1 Patient demographics (n=99)

Age (year)	
Mean±SD	60.6±11.0
Median (range)	61.0 (22–83)
KPS	
n	97
Mean±SD	77.7±13.4
Median (range)	80 (40–100)
Patients group	
Neurosurgery	6 (6.06 %)
Radiosurgery/gamma knife with or without whole brain radiotherapy	36 (36.36 %)
Whole brain radiotherapy	56 (56.57 %)
Symptom management (e.g. steroids)	1 (1.01 %)
Gender	
Female	56 (56.57 %)
Male	43 (43.43 %)
Primary cancer site	
Lung	53 (53.54 %)
Breast	22 (22.22 %)
Colon	6 (6.06 %)
Melanoma	6 (6.06 %)
Renal cell/kidney	5 (5.05 %)
Stomach	2 (2.02 %)
Liver	1 (1.01 %)
Ovarian	1 (1.01 %)
Testicular	1 (1.01 %)
Other	2 (2.02 %)
Patients coming from	
Outpatients	95 (95.96 %)
Inpatients	4 (4.04 %)
Location	
Radiotherapy clinic	77 (77.78 %)
Multidisciplinary brain metastases clinic	19 (19.19 %)
Hospital ward	2 (2.02 %)
Med oncology clinic	1 (1.01 %)
Married	
Married	70 (70.71 %)
Single	12 (12.12 %)
Widowed	6 (6.06 %)
Other	11 (11.11 %)
Cohabitants	
Spouse	43 (43.43 %)
Spouse and child(ren)	27 (27.27 %)
Alone	15 (15.15 %)
Child(ren)	8 (8.08 %)
Other	6 (6.06 %)
Education	
PhD or master	2 (2.11 %)
University (BSc/BA)	36 (37.89 %)
High school	41 (43.16 %)
Elementary school	5 (5.26%)
Other	11 (11.58%)
Employed	
Retired	49 (50.52%)
Employed	29 (29.90%)
Unemployed	19 (19.59%)
Number of brain metastases	
1	31 (32.98%)
2 to 3	35 (37.23%)
>3	28 (29.79%)
Previous systemic treatments	
Yes	59 (60.20%)
No	39 (39.80%)
Chemotherapy	
Yes	52 (76.47%)
No	16 (23.53%)
Hormone therapy	
Yes	11 (16.18%)
No	57 (83.82%)

by the National Cancer Institute of Canada policy requiring HRQOL to be incorporated into all their phase III trials unless otherwise indicated [17]. This change, which has been shown to be useful in determining the best treatments for patients and evaluating effects of treatment toxicity on patients [18], is also of benefit to evaluating treatments for advanced cancer patients of which HRQOL is the primary treatment endpoint. With such increasing importance placed on HRQOL, further emphasis is required to evaluate how to interpret this endpoint to ultimately assess treatments for patients. As such the application of MCID analysis is conducted to determine clinically accurate and substantial evaluations of treatments. The intention of our study was to determine the MCID in the EORTC QLQ-BN20 scales in brain metastases patients.

The most informative HRQOL questionnaires are disease-specific or condition-specific [18], an example of which is the EORTC QLQ-BN20. A literature search was conducted using the keywords “meaningful change” or “minimal clinically important difference” or “minimal important difference” and “neoplasm” or “cancer” to determine whether a similar research has been conducted in meaningful changes seen in patients with brain metastases. This is the first study evaluating MCIDs in the EORTC QLQ-BN20 for patients with brain metastases.

One other study was conducted by Maringwa et al. on MCIDs in the EORC QLQ-C30 and EORTC QLQ-BN20 for patients with primary brain cancer; this study included 941 patients and used the mini-mental status exam (MMSE) and World Health Organization performance status as an anchor. In their analysis, PS was used as a clinical anchor for the motor dysfunction scale from the BN20 and found that a 5.2-unit change in the scale represented clinically significant deterioration. Similarly, the MMSE was used as another anchor to determine the MCID for the communication deficit scale of the BN20, which found that 9.1-unit changes represented clinically significant improvement [11]. Although most similar to

Table 2 Baseline, follow-Up and changes in EORTC QLQ-BN20 scores and correlation with overall quality of life

	Spearman correlation (BN and overall QOL item)		Spearman correlation between changes in BN and changes in overall QOL item
	Baseline (n=99)	Follow-up (n=99)	
Future uncertainty	*−0.45*	*−0.48*	−0.17
Visual disorder	−0.28	−0.12	−0.17
Motor dysfunction	*−0.31*	−0.29	−0.11
Communication deficit	−0.09	−0.23	−0.080
Headaches	*−0.31*	−0.17	−0.051
Seizures	−0.012	−0.19	0.10
Drowsiness	−0.23	−0.27	−0.21
Hair loss	−0.0030	−0.28	0.10
Itchy skin	−0.078	−0.054	0.20
Weakness of legs	−0.22	−0.045	−0.081
Bladder control	−0.27	−0.27	−0.25

Italicized Spearman correlation coefficient indicates $r>|0.30|$

our current study, the findings in Maringwa et al.'s study differ from our current findings. This may be due to the difference in patient population and also the clinical anchors used.

In an analysis conducted by Bedard et al. in determining minimal important differences in advanced cancer patients using the EORTC QLQ-C15PAL, a sub-analysis was conducted on patients with different metastases. In patients with brain metastases, it was found that at 1-month follow-up, a change of 18.0 units in the scale of emotional functioning was statistically significant to represent clinically significant improvement using the overall QOL question as an anchor. A change of 27.2, 40.8 and 36.5 units in physical functioning, fatigue and pain, respectively, was required to represent a clinically significant improvement in patients [19]. Our study however, did not find any MCIDs for improvement in the EORTC QLQ-BN20 scales and symptoms.

MCID analyses have also been conducted in a general population of advanced cancer patients on a variety of symptoms and QOL assessments. However, due to the heterogeneity of patients included in the patient population, this could lead to a difference in MCIDs due to the symptom experience of patients with different sites of metastases. Bone metastases patients would be more likely to experience pain or bone pain, and brain metastases patients may be more likely to cite symptoms of fatigue [20]. Similar to our current investigation, Liang et al. have also conducted a MCID analysis on the EORTC QLQ-C30 and EORTC QLQ-BM22, which is the bone metastases module, to more specifically evaluate HRQOL in patients with bone metastases [21]. Comparably, our study is supported by the specificity of our patient population. However, these MCIDs are based on the clinical anchor used and are relative only to our chosen anchor.

The distribution-based MCID for the BN20 in brain metastases patients was close to the 0.5 SD. In accordance with our results, in a previous validation study by Norman et al. conducted in multiple studies using other QOL questionnaires, they found the 0.5 SD to be the closest value which represents most meaningful change [22].

Further investigation in MCID in the brain metastases population is useful to determine the required sample sizes for future brain metastases-related clinical trials by determining the required amount of patients to be treated [23]. This can also avoid the limitations of evaluating statistical significance in deciding treatment options.

In certain other studies, a larger magnitude of change has been found to be associated with meaningful improvement [13, 21]; however, other studies have also found the opposite: a larger magnitude of change is required to find a clinically meaningful deterioration [10, 24, 25]. Maringwa et al. have speculated that this may be attributed to subconscious physician bias in reporting stable or worsening PS, which ultimately explains why improvement requires greater QOL change [13]. However, our study avoids this possible bias through using a patient-reported clinical outcome in which patients themselves judge their QOL. This may explain why in our study, only meaningful change in deterioration was detected but not detected in patients who improved. Future studies may consider using such patient-reported clinical anchors as the patients themselves are most aware of their conditions, and such physician bias may also be avoided.

Limitations

A significant limitation to our current study is the small sample size. A larger sample size is required to reduce the possibility that the determined MCIDs for deterioration are not due to sampling variation and determine whether MCIDs for improvements exist. Our second limitation is the usage of one anchor (overall QOL) in our current study. Other conducted studies on MCIDs

Table 3 Minimal clinically important differences (MCIDs) for the EORTC QLQ-BN20 subscales—the mean (standard deviation) of patient's EORTC QLQ-BN20 scores categorized by their anchor status (improved, no change or deteriorated) and differences in the mean change scores (95 % CI) between adjacent categories (improvement is between "improvement" and "no change", and deterioration is between "deterioration" and "no change")

				MCID: difference in mean change (95 % CI)	
EORTC QLQ-BN20	Improvement of one unit in overall QOL (n=21)	No change in overall QOL (n=36)	Deterioration of one unit in overall QOL (n=20)	Improvement	Deterioration
Future uncertainty	−20.1 (25.5)	−9.0 (23.4)	−6.4 (31.9)	−11.2 (−24.5 to 2.2)	−2.6 (−17.5 to 12.4)
Vision disorder	−6.3 (15.1)	−7.0 (9.4)	−2.5 (16.6)	0.6 (−5.9 to 7.2)	−4.5 (−11.5 to 2.5)
Motor dysfunction	−2.1 (14.7)	−7.7 (15.4)	−3.3 (14.0)	5.6 (−2.8 to 14.0)	−4.4 (−12.7 to 4.0)
Communication deficit	−11.6 (21.5)	−5.2 (15.4)	−0.0 (15.7)	−6.4 (−16.2 to 3.4)	−5.2 (−13.9 to 3.4)
Headaches	−11.1 (30.4)	−6.5 (34.6)	−5.0 (22.4)	−4.6 (−22.9 to 13.6)	−1.5 (−18.7 to 15.8)
Seizures	0.0 (0.0)	−0.9 (5.6)	−7.0 (14.0)	0.9 (−1.5 to 3.4)	*6.1 (0.8 to 11.4)*
Drowsiness	−6.3 (29.1)	−1.0 (27.4)	11.7 (24.8)	−5.4 (−20.9 to 10.1)	−12.6 (−27.5 to 2.3)
Hair loss	17.9 (39.9)	15.9 (29.9)	12.1 (37.3)	2.0 (−21.8 to 25.8)	3.8 (−20.4 to 28.0)
Itchy skin	16.7 (21.1)	12.6 (25.8)	−2.4 (40.2)	4.0 (−11.2 to 19.3)	15.0 (−5.4 to 35.5)
Weakness of legs	−3.2 (31.5)	8.8 (25.0)	−5.0 (22.4)	−12.0 (−27.4 to 3.4)	*13.8 (0.2 to 27.4)*
Bladder control	−3.2 (14.5)	0.0 (16.2)	0.0 (15.3)	−3.2 (−11.8 to 5.5)	0.0 (−8.9 to 8.9)

Italicized MCID and 95 % CI indicated statistically significant differences between the mean change of the category

have utilized multiple anchors in the anchor-based approach. Thirdly, as suggested by Cella et al. and Crosby et al., the appropriateness of the anchor depends on the level of correlation between the QOL scales and the anchor [15, 26]. The anchors should also have at least a correlation of r>0.30 with HRQOL [14, 26]. However, in our correlation analysis, most scores had weak correlation with overall QOL at baseline or follow-up, except for future uncertainty, headaches and motor dysfunction. Although significantly correlated, the MCID estimates for future uncertainty, motor dysfunction and headache were not significant. The absence of strong correlation with the anchor may suggest that the chosen anchor is inappropriate for MCID estimates; however, other studies have also found moderately strong correlation at best between their chosen anchor and HRQOL scores, with the reason of this currently unknown [10, 11, 24]. As such our findings should be taken with caution. Due to the weak correlation with our chosen anchor, this advocates for further analyses with multiple anchors, especially since MCIDs are relative to the clinical anchor chosen [11]. Future studies should conduct MCID analysis in a larger population size with multiple anchors, such as KPS or changes in MMSE [11], to avoid such problems.

Table 4 Distribution-based approach to determine minimal important differences in the EORTC QLQ-BN20

	At baseline				At follow-up			
BN20	0.2 SD	0.3 SD	0.5 SD	SEM	0.2 SD	0.3 SD	0.5 SD	SEM
Future uncertainty	5.1	7.7	12.9	2.6	5.3	8.0	13.3	2.7
Vision disorder	3.1	4.6	7.7	1.6	2.8	4.2	7.0	1.4
Motor dysfunction	3.8	5.7	9.4	1.9	4.0	6.1	10.1	2.0
Communication deficit	4.0	5.9	9.9	2.0	3.2	4.7	7.9	1.6
Headaches	5.3	8.0	13.4	2.7	5.0	7.5	12.4	2.5
Seizures	3.1	4.6	7.7	1.5	2.5	3.7	6.2	1.2
Drowsiness	5.6	8.5	14.1	2.8	5.9	8.8	14.7	3.0
Hair loss	3.6	5.4	9.1	2.3	5.7	8.6	14.3	3.0
Itchy skin	4.2	6.2	10.4	2.3	5.3	7.9	13.2	2.7
Weakness of legs	5.0	7.5	12.4	2.5	6.3	9.5	15.8	3.2
Bladder control	4.0	6.0	10.1	2.0	4.2	6.3	10.5	2.1

Conclusion

In our current study, we determine the required change, which represents clinically meaningful change in the EORTC QLQ-BN20 in brain metastases patients undergoing treatment. Understanding MCIDs allows physicians to determine the impact of treatment on patients' QOL and sample sizes for clinical trials. Future studies should be conducted to validate in a larger population of patients with brain metastases.

Acknowledgments We thank the generous support of Dr. Mark Clemons, a participating investigator from The Ottawa Hospital Cancer

Centre in Canada and the Bratty Family Fund, Michael and Karyn Goldstein Cancer Research Fund, Pulenzas Cancer Research Fund, Joseph and Silvana Melara Cancer Research Fund and Ofelia Cancer Research Fund.

Conflict of interest None

References

1. Gavrilovic IT, Posner JB (2005) Brain metastases: epidemiology and pathophysiology. J Neurooncol 75(1):5–14
2. Bezjak A, Adam J, Barton R, Panzarella T, Laperriere N, Wong CS et al (2002) Symptom response after palliative radiotherapy for patients with brain metastases. Eur J Cancer 38(4):487–496
3. Tsao MN, Lloyd N, Wong RK, Chow E, Rakovitch E, Laperriere N et al (2012) Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev 4, CD003869
4. Patchell RA (2003) The management of brain metastases. Cancer Treat Rev 29(6):533–540
5. Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE et al (2012) Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol 2(3): 210–225
6. Mehta MP, Paleologos NA, Mikkelsen T, Robinson PD, Ammirati M, Andrews DW et al (2010) The role of chemotherapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 96(1): 71–83
7. Wong J, Hird A, Kirou-Mauro A, Napolskikh J, Chow E (2008) Quality of life in brain metastases radiation trials: a literature review. Curr Oncol 15(5):25–45
8. Leung A, Lien K, Zeng L, Nguyen J, Caissie A, Culleton S et al (2011) The EORTC QLQ-BN20 for assessment of quality of life in patients receiving treatment or prophylaxis for brain metastases: a literature review. Expert Rev Pharmacoecon Outcomes Res 11(6): 693–700
9. Jaeschke R, Singer J, Guyatt GH (1989) Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 10(4):407–415
10. Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA (2007) Interpreting clinically significant changes in patient-reported outcomes. Cancer 110(1):196–202
11. Maringwa J, Quinten C, King M, Ringash J, Osoba D, Coens C et al (2011) Minimal clinically meaningful differences for the EORTC QLQ-C30 and EORTC QLQ-BN20 scales in brain cancer patients. Ann Oncol 22(9):2107–2112
12. Neymark N, Kiebert W, Torfs K, Davies L, Fayers P, Hillner B et al (1998) Methodological and statistical issues of quality of life (QoL) and economic evaluation in cancer clinical trials: report of a workshop. Eur J Cancer 34(9):1317–1333
13. Maringwa JT, Quinten C, King M, Ringash J, Osoba D, Coens C et al (2011) Minimal important differences for interpreting health-related quality of life scores from the EORTC QLQ-C30 in lung cancer patients participating in randomized controlled trials. Support Care Cancer 19(11):1753–1760
14. Revicki D, Hays RD, Cella D, Sloan J (2008) Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol 61(2): 102–109
15. Crosby RD, Kolotkin RL, Williams GR (2003) Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol 56(5):395–407
16. Cella D, Eton DT, Fairclough DL, Bonomi P, Heyes AE, Silberman C et al (2002) What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) Questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study 5592. J Clin Epidemiol 55(3):285–295
17. Osoba D (1992) The Quality of Life Committee of the Clinical Trials Group of the National Cancer Institute of Canada: organization and functions. Qual Life Res 1(3):211–218
18. Osoba D (2002) A taxonomy of the uses of health-related quality-of-life instruments in cancer care and the clinical meaningfulness of the results. Med Care 40(6 Suppl):III31–III38
19. Bedard G, Zeng L, Zhang L, Lauzon N, Holden L, Tsao M, Danjoux C, Barnes E, Sahgal A, Poon M, Hicks K, Chow E (2013) Minimal important differences in the EORTC QLQ-C15-PAL to determine meaningful change in palliative advanced cancer patients. Asia Pac J Clin Oncol. doi:10.1111/ajco.12069
20. Fan G, Filipczak L, Chow E (2007) Symptom clusters in cancer patients: a review of the literature. Curr Oncol 14(5):173–179
21. Zeng L, Chow E, Zhang L, Tseng LM, Hou MF, Fairchild A et al (2012) An international prospective study establishing minimal clinically important differences in the EORTC QLQ-BM22 and QLQ-C30 in cancer patients with bone metastases. Support Care Cancer 20(12):3307–3313
22. Norman GR, Sloan JA, Wyrwich KW (2003) Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 41(5):582–592
23. Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS et al (2004) A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol 57(9): 898–910
24. Osoba D, Rodrigues G, Myles J, Zee B, Pater J (1998) Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 16(1):139–144
25. Cella D, Hahn EA, Dineen K (2002) Meaningful change in cancer-specific quality of life scores: differences between improvement and worsening. Qual Life Res 11(3):207–221
26. Cella D, Nichol MB, Eton D, Nelson JB, Mulani P (2009) Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy–Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. Value Health 12(1): 124–129