Is the EORTC QLQ-C30 emotional functioning scale appropriate as an initial screening measure to identify brain tumour patients who may possibly have a mood disorder?

Oort, Q.; Zwinkels, H.; Koekkoek, J.A.F.; Vos, M.J.; Reijneveld, J.C.; Taphoorn, M.J.B.; Dirven, L.

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ORIGINAL ARTICLE

Is the EORTC QLQ-C30 emotional functioning scale appropriate as an initial screening measure to identify brain tumour patients who may possibly have a mood disorder?

Quirien Oort[1] | Hanneke Zwinkels[2] | Johan A. F. Koekkoek[2,3] | Maaike J. Vos[2] | Jaap C. Reijneveld[1,4] | Martin J. B. Taphoorn[2,3] | Linda Dirven[2,3]

[1]Department of Neurology and Brain Tumor Center Amsterdam, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

[2]Department of Neurology, Haaglanden Medical Center, The Hague, The Netherlands

[3]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

[4]Department of Neurology, Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, The Netherlands

Correspondence
Quirien Oort, Department of Neurology and Brain Tumor Center Amsterdam, Amsterdam UMC, Vrije Universiteit Amsterdam, PO BOX 7057, 1007 MB, Amsterdam, The Netherlands.
Email: q.oort@amsterdamumc.nl

Abstract

Background: Screening glioma patients regularly for possible mood disorders may facilitate early identification and referral of patients at risk. This study evaluated if the EORTC QLQ-C30 Emotional Functioning (EF) scale could be used as an initial screening measure to identify patients possibly having a mood disorder.

Methods: EORTC QLQ-C30 EF and Hospital Anxiety and Depression Scale (HADS) scores were collected as part of a study assessing the impact of timing of patient-reported outcome assessments on actual health-related quality of life outcomes ($N = 99$). Spearman correlations and Mann-Whitney U tests were used to determine the association between the EF and HADS (sub)scales. Receiver Operating Characteristic analyses were performed to determine optimal cut-off EF scores to identify patients possibly having a mood disorder (i.e. HADS subscale score ≥8 points).

Results: EF and HADS (sub)scales correlated moderately (HADS-A: $r = -0.65$; HADS-D: $r = -0.52$). Significant EF score differences were found between patients with HADS ≥8 versus <8 points (HADS-A: mean difference (MD) = 32 and HADS-D: MD = 23). The EF scale had excellent (HADS-A; AUC = 0.88) and borderline excellent (HADS-D; AUC = 0.78) distinguishing capabilities. A statistically optimal (EF score <80) and a most inclusive (sensitivity of 100%, corresponding to an EF score <97) EF cut-off score correctly identified 88.0% and 96.0% of patients with a possible mood disorder, respectively.

Conclusion: EORTC QLQ-C30 EF scale seems to be an appropriate screening measure to identify glioma patients possibly having a mood disorder in need of further assessment.

KEYWORDS
affective symptoms, anxiety, brain tumour, cancer, depression, emotional functioning, EORTC QLQ-C30, HADS, oncology

1 | INTRODUCTION

Anxiety and depression may have a detrimental effect on a patient's perceived quality of life.[1] Affective symptoms and disorders are not uncommon among brain tumour patients, and can be present at any time throughout the course of the disease. Despite advances in therapies that offer improved (progression-free) survival rates, a brain tumour remains an incurable and progressive oncological and neurological disease. It has been suggested that mood disorders are associated with the patients' reaction to the losses related to a diagnosis of brain cancer or to chemical imbalances in the brain resulting from the glioma metabolism, or both.[2-4] More than half of primary brain tumour patients reported symptoms of anxiety as well as a self-reported anxiety disorder before and 1 year after surgery,[5] and 48% of patients visiting routine neuro-oncology outpatients' clinic were found to have a generalized anxiety disorder.[6] Moreover, 41% of patients visiting the neuro-oncology outpatient clinic were found to have major depressive disorder (MDD),[6] which often occurs 6 months after starting radiotherapy and persisting for at least 3 months.[7] The prevalence of MDD was found to be higher in brain tumour patients (28%)[8] compared with patients with other types of cancer [ranging: 6%–13%].[9]

Screening glioma patients regularly for presence of anxiety and depressive symptoms may facilitate early identification of patients who may possibly have a mood disorder, and may be an indication for referral and treatment, if needed. As previous research has shown that anxiety and depression are not always accurately recognised by healthcare professionals, routine screening for the symptoms of anxiety and depression indeed may be valuable to better recognize patients at risk.[10] This is supported by the finding that physicians' reports of depression, as scored on the SF-36 questionnaire, were highly discordant with patients' reports of clinically significant depression, with physicians reporting depression less frequently than patients did.[11]

More routinely implemented patient-reported outcomes in neuro-oncological clinical care are typically multi-dimensional health-related quality of life (HRQoL) questionnaires,[12] such as the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30)[13] or the Functional Assessment of Cancer Therapy-Brain (FACT-Br).[14] Although these questionnaires have an emotional well-being/functioning scale, due to the multi-dimensionality of the questionnaires these scales typically comprise a few questions only. The Hospital Anxiety and Depression Scale (HADS)[15] is a more in-depth patient-reported screening measure, comprising 14 questions related to symptoms of anxiety and depression, and is therefore better suited to detect possible anxiety or depressive disorders. However, assessment of both the HADS and a HRQoL questionnaire would increase the patient burden, while not being relevant for all patients. Ideally, more in-depth assessment with the HADS to assess the possible presence of anxiety or depressive disorder in clinical practice should only be performed in those patients that more likely to suffer from report affective symptoms. A study in 5217 glioma patients showed that the mean score on the EORTC QLQ-C30 EF scale was 71 shortly after diagnosis,[16] slightly lower than the general population in which a mean score of 74 was found,[17] and that 17% of glioma patients did not report any problems with EF.[16] It is therefore hypothesized that for a reasonable proportion of glioma patients it is not needed to perform a more in-depth assessment with the HADS.

This study aimed to evaluate if the EORTC QLQ-C30 emotional functioning (EF) scale can be used as an initial screening measure in brain tumour patients to identify those patients who may possibly have a mood disorder. Secondly, it was evaluated if further assessment with the HADS is warranted in all patients without a perfect score on the EF scale.

2 | METHODS

2.1 | Patient population

Data was collected as part of a randomized prospective study measuring the impact of the timing of patient-reported outcome assessments on the actual HRQoL outcomes in clinical care for glioma patients.[18] Patients were recruited in the Haaglanden Medical Center in The Hague, The Netherlands, between July 2016 and July 2018. Informed consent was obtained from all patients and their proxies included in the study. The patient population consisted of a consecutive sample of adult patients with a histologically confirmed grade II-IV glioma according to the World Health Organisation (WHO) 2016 classification criteria. Patients were eligible if no progression was observed on previous imaging, and were scheduled for a follow-up MRI and a corresponding consultation with the treating physician to discuss the MRI results. No data was recorded on the response rate and reasons for non-participation.

2.2 | Study design

Patients were requested to complete the EORTC QLQ-C30[13] and brain cancer module (QLQ-BN20),[19] and the HADS[15] at two time points: 1) on the day of the MRI scan and 2) at the day of the consultation with the physician to discuss the MRI results. During the second assessment, patients were randomly assigned to one of two groups: questionnaires were administered 1) *before* the consultation with the physician or 2) *after* the consultation with the physician. Further details on the study design and outcomes are described previously.[18] For this study, the outcomes of the first assessment (day of the MRI scan) were used for the primary analyses. The data of patients with both a EORTC QLQ-C30[13] and HADS[15] measurement during the first assessment were extracted from the original study. Data of the second assessment was used for a sensitivity analysis to assess the accuracy of the cut-off scores determined with data of the first assessment. As no differences in main study outcomes were found between the randomised groups (i.e. second measurement before or after the consult with physician),[18] patients were analysed together.

2.3 | Instruments

The EORTC QLQ-C30 and QLQ-BN20 are patient-reported outcome measures assessing HRQoL of cancer patients and brain tumour patients specifically, and comprise both single- and multi-item scales. The Emotional Functioning (EF) scale of the EORTC QLQ-C30 consists of four items regarding feeling tense, worrying, feeling depressed, and being irritable, scored on a 4-point Likert scale ranging from 'not at all' to 'very much'. Thus, the EF scale measures aspects of anxiety and depression and general distress, and is assumed to represent an unidimensional construct.[20] Raw EF scale scores are linearly transformed, as described in the EORTC Scoring Manual,[21] into an EF scale score ranging from 0 to 100, with higher scores representing better emotional functioning.

The HADS is a 14-item self-reported screening measure to detect the possible presence of anxiety and depressive states in a hospital medical outpatients' clinic setting. It has been found valid and reliable in cancer patients[22] and is regularly implemented in studies with brain tumour patients.[22-27] The HADS comprises an Anxiety (HADS-A) and a Depression (HADS-D) subscale. Both scales consist of seven items which are scored on a 4-point Likert scale [0–3]. Scores of both scales range from 0 to 21, with scores between 0 and 7 regarded as being in the normal range, scores between 8 and 10 suggesting the possible presence of anxiety or depression, and scores of ≥11 indicating a probable presence of a mood disorder.[28] This study examined all patients that may possibly have a mood disorder (i.e. patients with a score of ≥8 on one or both HADS subscales).

2.4 | Statistical analyses

Descriptive statistics were used to describe the sociodemographic and clinical characteristics of the patient population. IBM SPSS version 26.0 was used to carry out all statistical analyses,[29] and a *p*-value <0.05 was considered statistically significant.

First, to determine the correlation between EF score and the subscale scores of the HADS, Spearman correlations were calculated. In accordance with Dancey & Reidy (2007),[30] correlations between 0.0 and 0.3 were considered as weak, 0.4–0.6 as moderate, 0.7–0.9 as strong, and 1.0 as perfect. Mann-Whitney U tests were performed to establish if there were significant and/or clinically meaningful differences on EF scores between patients that possibly may and probably do not have a mood disorder (HADS-A or HADS-D score ≥8 vs. <8 points, respectively). The between-group minimally important differences (MIDs) of the EF scale for glioma patients of four points difference[31] was used to determine clinically meaningful differences.

To determine the optimal EF scale cut-off score to identify brain tumour patients that may possibly having a mood disorder (i.e. score of ≥8 on the HADS-A or HADS-D subscale, respectively), a receiver operating characteristic (ROC) analysis was performed, and the area under the curve (AUC) was calculated to investigate the association between sensitivity and specificity. Furthermore, positive and negative predictive values were calculated (i.e. PPV and NPV). High sensitivity corresponds to high negative predictive value.[32] ROC curves plot sensitivity versus 1-specificity, enabling visualization of the optimal EF scale cut-off to distinguish patients that may and may not possibly have a mood disorder (i.e. score of ≥8 vs. <8 points on HADS-A or HADS-D subscale, respectively). In general, an AUC value of 0.6–0.7 was considered poor, between 0.7 and 0.8 as acceptable, between 0.8 and 0.9 as excellent, and above 0.9 as outstanding.[33,34] Both the optimal statistical cut-off (defined as the optimal balance between sensitivity and specificity) as well as a cut-off that was most inclusive (defined as including all patients with a HADS scale score of ≥8 points, i.e. sensitivity of 100%) were determined. In both cases, emphasis was laid on high sensitivity to retain as many patients with a possible mood disorder and only "exclude" patients who probably do not need to be further assessed. The cut-off scores determined using data of the first assessment (at the day of the MRI scan; primary dataset) were subsequently applied on the available dataset of the second assessment (at the day of the consult with the physician; validation dataset), as a sensitivity analysis.

3 | RESULTS

In the original study, $N = 100$ patients were analysed. The HADS subscales scores of the first assessment was missing for one patient and therefore excluded in this study. Sociodemographic and clinical characteristics of the $N = 99$ participating patients are described in Table 1.

Results showed that there were 23 patients (23%) with an EF score of 100 ('no problems'), and 13 (13%) and 11 (11%) patients indicating no problems on the HADS Anxiety and Depression scale, respectively. The scores on the EF and HADS (sub)scales, separately for this with a normal score (0–7) and possible cases (≥8), during the first assessment are presented in Table 2. As expected, the mean EF scale score was poor for patients that may possibly have a mood disorder, compared to patients with HADS scores in the normal range. There were only two patients with a probable anxiety disorder (i.e. HADS-A score of ≥11) and only four with a probable depressive disorder (i.e. HADS-D score of ≥11) [further details not shown].

The EF scale score correlated moderately with the HADS-A ($r = -0.65$, $p < 0.00001$) and HADS-D ($r = -0.52$, $p < 0.00001$) subscale scores. Patients that may possibly have anxiety disorder (i.e. score of ≥8 points) had a significantly (mean rank (MR) = 19 versus MR = 57, $p < 0.001$) lower EF scale score than patients with HADS-A scores in the normal range. Similarly, patients that may possibly have a depressive disorder (i.e. score of ≥8 points) had a significantly (MR = 26 vs. MR = 54, $p < 0.01$) lower EF scale score, than patients with HADS-D scores in the normal range. In both cases, these

TABLE 1 Patients' sociodemographic and clinical characteristics

Participants, *N*	99
Sex (male), *N* (%)	58 (57%)
Age, mean (SD)	55.6 (12.5)
Level of education, *N* (%)	
Lower	55 (56%)
Higher	44 (44%)
Tumour type, *N* (%)	
Diffuse astrocytic and oligodendroglial tumours	
WHO grade II glioma	45 (45%)
WHO grade III glioma	9 (9%)
WHO grade IV glioma	42 (42%)
Ependymal tumours	
WHO grade II	1 (1%)
Other	2 (2%)
Time since diagnosis (months), median [range]	28 [6–298]
KPS score, median [range]	90 [60–100]
State of disease, *N* (%)	
Stable disease	77 (78%)
Tumour progression	20 (20%)
End of life phase	2 (2%)
Time between HRQoL assessments (days), mean (SD)	7 (5)

Notes: Level of education in accordance with international standard classification of education[35] [range 0–8], with scores between 0 and 4 considered as lower education and scores between 5 and 8 as higher education.

Abbreviations: KPS, Karnofsky Performance Status; SD, standard deviation.

differences were found to be clinically relevant, with a mean difference of 32 (95% CI: 22–42) and 23 (95% CI: 11–36) for anxiety and depression, respectively.

3.1 | Optimal EF scale cut-off score to identify patients possibly having a mood disorder

3.1.1 | Primary dataset

The ROC curves including the EF scale score and HADS-A and HADS-D scores (detection of patients with score ≥8 or <8 points) are depicted in Figure 1a,b. The AUC of the EF score with the HADS-A score was 0.88 (Standard Error (SE) = 0.04, Confidence interval (CI) 95% = 0.80–0.96, $p < 0.001$), which is classified as excellent. The AUC for the HADS-D score was classified as acceptable (AUC = 0.78, SE = 0.07, CI-95% = 0.64–0.92, $p < 0.01$). The sensitivity, specificity, positive predictive and negative predictive values per EF scale cut-off score are presented in Table 3. The statistically optimal cut-off score for implementing the HADS was determined to be an EF scale score <80, irrespective of scale. The most inclusive cut-off score (i.e., highest possible sensitivity) was an EF scale score <97, suggesting that any deviation from a perfect score on the EF scale would constitute implementing the HADS. Even with this cut-off score, some patients with depressive symptoms might be missed (i.e., sensitivity of 93%).

TABLE 2 HADS scale scores and Emotional Functioning (EF) scale scores during the first assessment (i.e. test sample)

	Normal range (score <8)	Possible cases (score ≥8)	Total
HADS-A			
Number of patients	81	18	99
Mean (SD)	3 (2)	10 (2)	4 (3)
Median	3	9	3
Range	0–7	8–16	0–16
EF score, Mean (SD)	83 (18)	51 (23)	77 (23)
HADS-D			
Number of patients	85	14	99
Mean (SD)	3 (2)	10 (2)	4 (3)
Median	2	10	3
Range	0–7	8–15	0–15
EF score, M (SD)	81 (20)	57 (26)	77 (23)

Abbreviations: A, anxiety subscale; D, depression subscale; EF, emotional functioning; HADS, Hospital Anxiety and Depression Scale; M, mean; SD, standard deviation.

3.1.2 | Validation dataset

Applying the determined statistically optimal cut-off (EF < 80) in the available dataset of the second assessment showed that for the HADS-A, the cut-off score correctly identified 94.4% (17/19) of patients with a possible anxiety disorder. For the HADS-D, the statistically optimal cut-off correctly identified 85.7% (12/14) of patients with a possible depressive disorder. Altogether, there were 25 patients with a possible mood disorder. The statistically optimal cut-off score correctly identified 88.0% (22/25). However, there were 44 patients who scored EF < 80 and half of the patients (50.0%; 22/44) would have 'unnecessarily' filled in the HADS.

The most inclusive cut-off correctly identified 100.0% (18/18) of the patients with a possible anxiety disorder and 92.9% (13/14) of the patients with a possible depressive disorder. Altogether, this cut-off correctly identified 96.0% (24/25) of patients with a possible mood disorder. On the other hand, as optimal sensitivity was selected for this cut-off, there were 74 patients who scored EF < 97. This

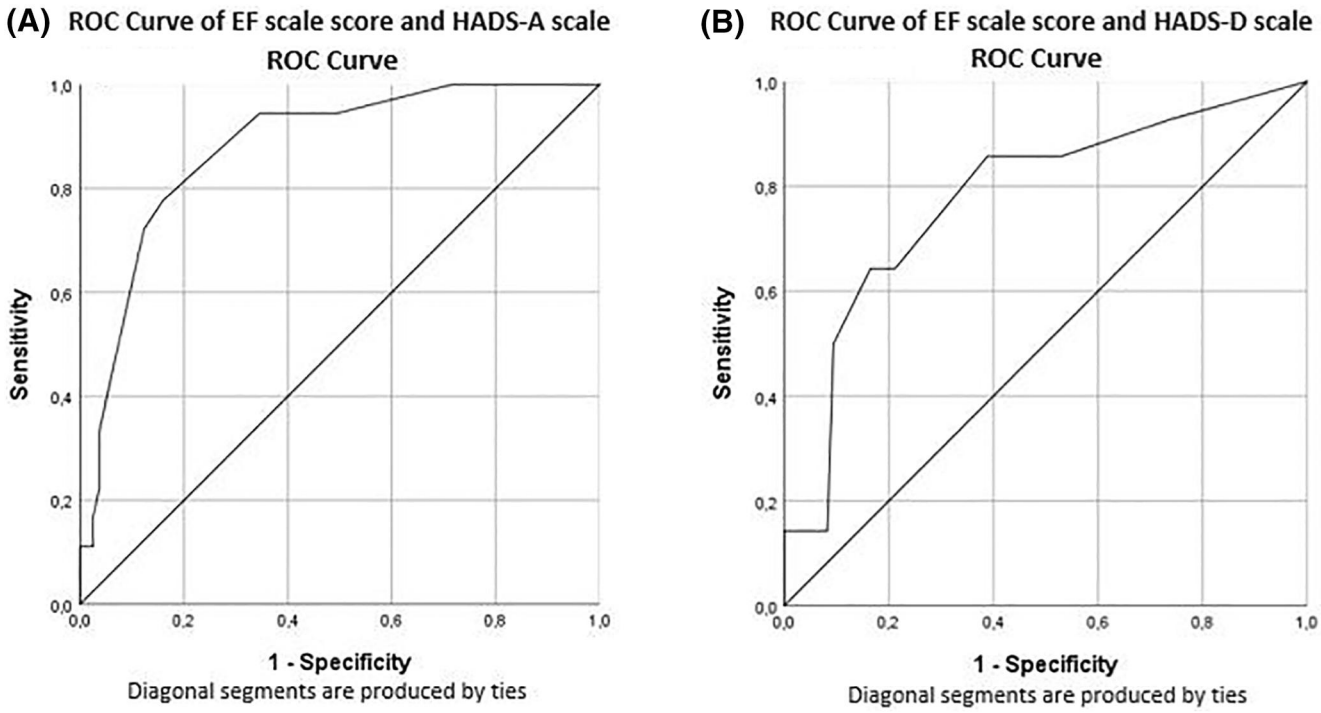

FIGURE 1 ROC curves including the EORTC QLQ-C30 Emotional Functional scale score and HADS Anxiety score (A) and HADS Depression score (B)

TABLE 3 Sensitivities, specificities, positive predictive value and negative predictive value percentages per EF scale cut-off scores

EF scale	HADS-A score ≥8				HADS-D score ≥8			
Linearly transformed cut-off score	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
≤96	100	28	24	100	93	26	17	96
≤88	94	51	30	98	86	47	21	95
≤79	94	65	38	98	86	61	27	96
≤71	78	84	52	94	64	79	33	93
≤63	72	88	57	93	64	83	39	93
≤54	50	93	60	89	50	91	47	92
…								

means that 67.6% (50/74) of the patients scoring below the most inclusive EF cut-off score would have 'unnecessarily' filled in the HADS.

4 | DISCUSSION

In line with results from previous studies, self-reported affective symptoms were not uncommon in this study's glioma population. Results showed that almost a third (26%) of the patients may possibly have a mood disorder (i.e. HADS subscale score ≥8 points). The average EF scale score of 77 in this study was comparable to that of glioma patients participating in clinical trials (N = 3708; M = 72),[16] but considerably lower than that of the Dutch general population (N = 1731; M = 89),[36] but similar to an European population (15,386, M = 74).[17] Screening for patients who may possibly have a mood disorder or presence of affective symptoms could be highly valuable to eventually improve their HRQoL, which is particularly important in patients with a brain tumour given the incurable nature of the disease.

To effectively screen for patients who may suffer from a mood disorders without unnecessarily increasing the patient burden, this study aimed to evaluate if the commonly assessed EF scale of the EORTC QLQ-C30 questionnaire could be used in neuro-oncological clinical practice as a screening measure to identify patients in need of more in-depth assessment of emotional well-being with the HADS questionnaire. Similar to our study, studies in other populations have previously found significant correlations of moderate strength

between the EF scale scores and the HADS subscale scores, for example in gastrointestinal cancer patients,[37] a large Norwegian cancer patient population[38] and advanced cancer patients.[39] Furthermore, our results showed that patients who may possibly have a mood disorder scored statistically significant as well as clinically relevant lower on the EF scale than patients with scores in the normal ranges of the HADS subscales. This finding demonstrates that the two measures have concurrent validity and assess the same underlying affective construct.

ROC analyses were performed to determine if the EF scale can accurately discriminate between patients with and without a possible mood disorder. A literature review showed that the HADS subscale score threshold of ≥8 points showed an optimal balance between sensitivity and specificity, as a case finder for mood disorders in the general population and in patients with cancer or other somatic illnesses.[40] ROC analyses in our study showed that the EF scale appeared to be excellent[33,34] at distinguishing between patients with a score of ≥8 versus <8 points on the HADS-A subscale, and acceptable[33,34] at distinguishing between patients with a score of ≥8 versus <8 points on the HADS-D subscale. However, the AUC of 0.78 for the HADS-D subscale might arguably be seen as borderline excellent (excellent is defined as ≥0.80). The statistics support the notion that the EF scale is an appropriate screening measure for patients in need of further assessment of both anxiety and depression, for which the HADS could be used, but potentially also other measures. The finding that the EF scale might not be excellent in distinguishing between cases with ≥8 points on the HADS-D subscale may be due to the fact that the EF scale only contains the items '*Have you felt depressed?*', '*Have you felt tense?*', '*Have you worried?*' and '*Have you felt irritable?*', and does not address the more depression specific symptoms regarding to loss of interest and enjoyment, which are prominently included in the HADS-D subscale.

5 | CLINICAL IMPLICATIONS

As there are currently psychological care and interventions available to improve the psychological well-being of brain tumour patients,[41-43] it is important to identify which patients in a clinical practice setting might benefit. This study determined two EF cut-off scores to identify patients possibly having a mood disorder, a statistically optimal cut-off score and a cut-off score that was most inclusive (i.e., including all patients with any reported symptoms). Although the statistically optimal cut-off score is used to balance sensitivity and specificity when identifying patients possibly having a mood disorder, this resulted in the lack of identification of three patients who may possibly have a mood disorder in the second dataset. One of these patients even reported considerably high levels of anxiety (HADS-A = 11). When implementing the statistically optimal EF cut-off score, frequent screenings would be recommended in order not to overlook any patients possibly in need of psychological assistance. The most inclusive cut-off score missed only one patient who may possibly have had a mood disorder in the second dataset. However, this cut-off suggests that any deviation from a perfect score on the EF scale would constitute implementing the HADS scale for further assessment of possible anxiety or depressive symptoms, and would, as hypothesized, result in a considerably lower specificity and a relatively higher amount (+28%) of patients 'unnecessarily' filling in the HADS questionnaire. Nevertheless, this more stringent cut-off could be useful if there is less frequent screening, particularly when considering that the benefits of possible necessary psychological care will outweigh the time investment in completing the HADS (approximately 2–5 min[28]). Alternatively, a stepped care model, a framework describing referral to different levels of intervention appropriate to each patient based on screening and triage,[44] could be appropriate. In this case, patients with a EF score <97 but ≥80 would be contacted by a specialized health care professional to further discuss the issue, and patients with a EF score <80 would get a more in-depth psychological assessment.

6 | STUDY LIMITATIONS

Although a HADS subscale cut-off score of ≥8 points is seen as an optimal case finder for mood disorders in different patient populations,[40] it is still unclear at what exact level of psychological distress brain tumour patients would require psychological care and interventions. Possibly, only patients with more severe levels of psychological distress may benefit from psychological care. This would imply that a more stringent EF cut-off score (i.e., the clinical optimal cut-off score for patients with a HADS subscale score of ≥11 points) is more efficient in detecting patients in need of psychological care. Unfortunately, the number of patients with HADS subscale scores of ≥11 was too small in this study to determine an EF cut-off score to detect patients with a probable mood disorder. Nevertheless, the current study mainly aimed to determine if the EORTC QLQ-C30 EF scale is suitable to screen patients for affective symptoms who possibly have a mood disorder, warranting further investigation and perhaps additional attention from the professional caregivers. Furthermore, the level of anxiety and depression in this study may be an overestimation, because these outcomes were assessed at time points that may have increased the patients' levels of anxiety and depression,[18] namely during an MRI scan and the day of the consultation with the physician. The phenomenon "scanxiety", that is heightened scan-associated state of psychological distress, has been previously established in other cancer populations.[45] Future studies should investigate the usefulness of the cut-off score in a larger sample and particularly at different time points during the disease course.

In conclusion, the EORTC QLQ-C30 EF scale seems adequate as screening measure for identifying patients who may possibly have a mood disorder, and thus require further assessment. The statistically optimal cut-off score is the most accurate at distinguishing patients with and without a possible mood disorder, however, does occasionally miss patients. The most inclusive cut-off score is much more conservative and would currently be recommended in a clinical practice setting with less frequent screenings using the EORTC

QLQ-C30 EF scale in order not to overlook any patients possibly in need of psychological assistance.

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CONFLICT OF INTEREST

None of the authors declares a conflict of interest.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was conducted in accordance with the Declaration of Helsinki. A declaration of no-objection was granted by the medical ethical review board of the institution (METC Zuidwest Holland, ethic code '2016-062').

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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