Effects of Radiotherapy for Brain Metastases on Quality of Life (QoL)

Prospective Pilot Study of the DEGRO QoL Working Party

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Background: Prospective data on quality-of-life (QoL) effects of radiotherapy for brain metastases are currently lacking, but would be of great interest to guide therapeutic decisions.
Patients and Methods: From 01/2007 to 08/2007, 46 patients with previously untreated brain metastases were recruited at eight centers. QoL was measured at start of treatment (T_0) and at 3 months (T_{3mo}). In the pilot study, two combinations of QoL instruments could be used at the discretion of the centers (A: EORTC QLQ-C30 and B: EORTC QLQ-C15-PAL both with brain module BN20, assessment by proxies with A: Palliative Care Outcome Scale, B: self-constructed brain-specific instrument).
Results: All patients received whole-brain radiotherapy, four with an additional boost irradiation. At T_{3mo}, 26/46 patients (56.5%) had died. 17/20 survivors (85%) completed the questionnaires. In 3-month survivors, QoL deteriorated in most domains, significant in drowsiness, hair loss and weakness of legs. The scores for headaches and seizures were slightly better after 3 months. Assessment by proxies also suggested worsening of QoL. Initial QoL at T_0 was better in those alive than in those deceased at T_{3mo}, significant for physical function and for the symptom scales of fatigue and pain, motor dysfunction, communication deficit and weakness of legs.
Conclusion: Practicability and compliance appeared better with the (shorter) version B. This version is now used in the ongoing main phase of the study with additional centers. First results indicate a moderate worsening of QoL during the first 3 months after start of palliative radiotherapy for brain metastases. QoL at initiation of radiotherapy may be prognostic for survival.

Key Words: Quality of life · Brain metastases · Radiotherapy

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Lebensqualitäts-(LQ-)Effekte der Strahlentherapie von Hirnmetastasen. Prospektive Pilotstudie des DEGRO-LQ-Arbeitskreises

Hintergrund: Prospektive Daten über die Auswirkung einer palliativen Strahlentherapie auf die Lebensqualität (LQ) von Patienten mit Hirnmetastasen existieren nur wenige, jedoch sind sie von großem Interesse für Therapieentscheidungen.
Patienten und Methodik: Von 01/2007 bis 08/2007 wurden an acht Zentren 46 Patienten mit bisher unbehandelten Hirnmetastasen rekrutiert (Tabelle 1). Die LQ vor und 3 Monate nach palliativer Strahlentherapie wurde erhoben. In der Pilotphase konnten die Zentren zwischen zwei Kombinationen von Instrumenten wählen (A: EORTC QLQ-C30 und B: QLQ C15-PAL jeweils mit Hirnmodul BN20, Fremdeinschätzung durch Angehörige mittels A: Palliative Care Outcome Scale, B: eigenen Hirnmoduls).
Ergebnisse: Alle Patienten erhielten eine Ganzhirnbestrahlung, vier Patienten zusätzlich eine Boostbestrahlung. 3 Monate nach Therapiebeginn waren 26/46 Patienten (56,5%) verstorben. Die Rücklaufquote der Fragebögen der Überlebenden betrug 17/20

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(85%). Für dieses Kollektiv der 3-Monats-Überlebenden zeigte die Selbsteinschätzung eine Verschlechterung in den meisten Bereichen, signifikant für Schläfrigkeit, Alopezie und Beinschwäche. Die Scores für Kopfschmerzen und Krampfleiden waren nach 3 Monaten etwas besser (Abbildung 1). Die Fremdeinschätzungen zeigten ebenfalls eine zunehmende Beeinträchtigung der Patienten nach 3 Monaten (Abbildung 2). Die initiale LQ war bei den 3-Monats-Überlebenden (Abbildung 3a) im Vergleich zu den Verstorbenen besser, signifikant für die körperliche Funktion und für die Symptomskalen Fatigue, Schmerz (Abbildung 3b), motorische Dysfunktion, Kommunikationsdefizit und Beinschwäche (Abbildung 3c).

Schlussfolgerung: Die kürzere Fragebogenvariante B schien bezüglich der Praktikabilität und Compliance besser zu sein. Demzufolge wird diese Variante in der aktuell laufenden Hauptphase mit zusätzlichen Zentren verwendet (Abbildung 4). Erste Ergebnisse deuten auf eine mäßige LQ-Verschlechterung bei 3-Monats-Überlebenden hin. Möglicherweise könnte die initiale objektivierte LQ als prädiktiver Faktor herangezogen werden.

Schlüsselwörter: Lebensqualität · Hirnmetastasen · Strahlentherapie

Introduction

Quality-of-life (QoL) measurement becomes more and more relevant in clinical practice. QoL as an additional endpoint is standard in clinical phase III trials and knowledge of posttherapeutic QoL is essential for appraisal of different therapeutic options. Results of QoL enhance patient participation in the treatment process [4, 21]. Palliative therapy courses should aim to improve or at least stabilize QoL.

Brain metastases continue to portend a poor prognosis with survival in the 2- to 4-month range [23]. Different treatment concepts are available for radiotherapy of brain metastases [8, 17–19]. Specific interventions such as whole-brain radiotherapy (WBRT), with or without boost, and radiosurgery have distinct therapeutic effects and may results in a specific development of QoL. Only a limited number of investigators have assessed QoL in the context of patients suffering from brain metastases [20].

The use of QoL outcomes also could provide prognostic information, like recent studies have shown for survival in cancer patients [13]. They could identify patients who will benefit from a specific intervention and prevent overtreatment of patients who will gain no advantage from aggressive therapy. Only few studies have examined QoL and/or cognitive functioning as a prognostic factor in brain cancer [5, 12, 15, 16, 20].

Therefore, we prospectively assessed QoL in patients treated with radiotherapy for brain metastases, using – in a pilot phase – two sets of standardized QoL questionnaires, each complemented by variants of instruments for QoL assessment by proxies.

Patients and Methods

Patient and Treatment Characteristics

From 01/2007 to 08/2007, 46 patients with previously untreated brain metastases were recruited at eight centers for this pilot phase of a multicenter QoL study. The dominant radiotherapy strategy was WBRT alone. Four patients additionally received boost irradiation. Patient and treatment characteristics, including the pretreatment Karnofsky performance status and the Barthel Index, a scale summarizing the ability to perform activities of daily living, are presented in Table 1.

Quality-of-Life Questionnaires

QLQ-C30, QLQ-C15-PAL and BN20 instruments were developed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Study Group for measuring the QoL of cancer patients in clinical trials [1]. The QLQ-C30 contains 30 items and covers the domains of physical, role, emotional, cognitive, and social function as well as global health status (multi-item scales) and several symptoms. Each item is scored from 1 to 4 ("not at all": 1; "a little": 2; "quite a bit": 3; "very much": 4). As an exception, global QoL is scored from 1 ("very poor") to 7 ("excellent"). QLQ-C15-PAL is a shortened form of QLQ-C30 for use in a palliative-care setting, containing 15 items for the following nine domains [11]: physical function, emotional function, global QoL, pain, fatigue, appetite, dyspnea, constipation, and sleep. The results for these domains are directly comparable between QLQ-C30 and QLQ-C15-PAL [11].

The BN20 questionnaire is a brain-specific module to be used in conjunction with QLQ-C30 and contains 20 items, grouped into four domains (future uncertainty – four items, visual disorder, motor dysfunction and communication deficit – three items each) as well as seven single items (headaches, seizures, drowsiness, hair loss, itchy skin, weakness of legs, bladder control).

Questionnaire data were processed according to the procedures outlined in the EORTC QLQ-C30 scoring manual [9]. For functional scales and global QoL, high scores represent good functioning/good QoL. For the symptom scales and for all scales of BN20, high scores indicate severe symptoms.

To permit assessment of QoL in patients with massive deterioration of QoL, evaluation by proxies, i.e., close relatives, was included. Two alternative questionnaires were employed: the Palliative Care Outcome Scale (POS), an established, but not brain-specific instrument for evaluation of patients in a palliative-care setting [2]. For this instrument, each of ten items is scored on a scale from 0 to 4, the maximum total score of 40 equals maximum impairment. To specifically address the proxy assessment of QoL in patients with brain metastases, a ten-item questionnaire was developed focusing on relevant areas and denoted DEGRO-LQ brain module (Appendix 1).

Table 1. Baseline clinical and treatment characteristics of 46 patients with previously untreated brain metastases registered for prospective quality-of-life assessment. RPA: recursive partitioning analysis.

Tabelle 1. Klinische Charakteristika und Behandlungsdaten der Patienten (n = 46), die zur Erhebung der Lebensqualität in die Untersuchung eingeschlossen wurden. RPA: „recursive partitioning analysis".

Age (years)	**Median (range)** **Total**	**61 (33–84)** **n = 46** **Patients (n)**	**100%** **(%)**
Primary tumor	Non-small cell lung cancer	19	42
	Small cell lung cancer	4	9
	Melanoma	3	7
	Renal cell carcinoma	4	9
	Colorectal cancer	2	4
	Breast cancer	9	20
	Others	4	9
RPA classification	I	3	7
	II	34	74
	III	9	20
Karnofsky performance status	80–100	22	48
	< 80	24	52
Barthel Index	90–100	34	74
	< 90	12	26
Fractionation of whole-brain	10 × 3 Gy	31	68
radiotherapy	20 × 2.25 Gy	5	11
	Others	10	21
Initial steroid dose	Daily dose < 50 mg	28	61
(prednisone equivalent)	Daily dose 50–100 mg	13	28
	Daily dose > 100 mg	5	11
Extracranial tumor status	Primary tumor not detectable	19	41
	Primary tumor detectable, not progressive	7	15
	Primary tumor progressive	20	44
	Any extracranial metastases	37	80

Each item was scored with 0 to 10 points, resulting in a total score of 0–40, 40 is equal to an optimal QoL.

Questionnaire Administration

In this pilot phase of a multicenter study, individual centers selected one of two combinations of questionnaires: (A) EORTC QLQ-C30 with brain module BN20 and proxy assessment with POS or (B) EORTC QLQ-C15-PAL with BN20 and proxy assessment with DEGRO-LQ brain module. Questionnaires were handed out to the patients at the time of information about the planned radiotherapy. At this time, patients gave written informed consent to participate in the QoL study. Ethics approval was obtained from the ethics committee at the University of Würzburg, Germany. 3 months after the first radiotherapy session, survival status of patients was determined and patients not known to have died were mailed the respective set of questionnaires.

Statistical Analysis

Overall survival (OS) were calculated using the Kaplan-Meier method. Survival differences between subgroups were evaluated using the log-rank test ($p < 0.05$ considered significant).

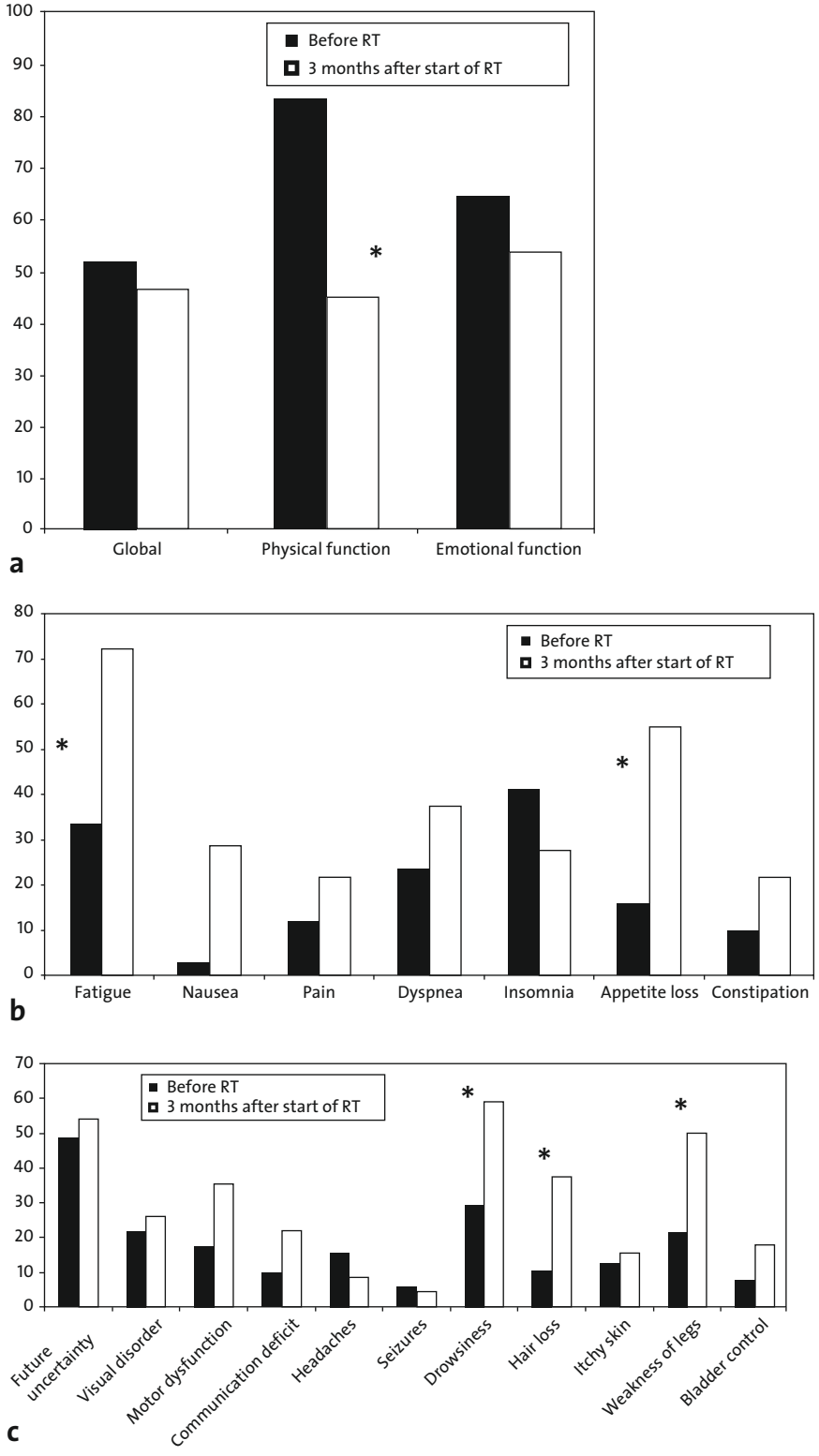
QoL results are presented as mean scores and were compared between time points and between subgroups of patients using the Mann-Whitney U-test ($p < 0.05$ considered significant). Patients were grouped as follows, according to the known prognostic recursive partitioning analysis (RPA) classification of the Radiation Therapy Oncology Group (RTOG) [10]: class I: patients with Karnofsky Performance Score (KPS) ≥ 70, < 65 years of age and with controlled primary and no extracranial metastases; class III: KPS < 70; class II: all others.

Results

3 months after beginning of radiation therapy, 26 of 46 patients had died (56.5%). According to RPA classification, class I included three, class II 34, and class III nine patients. The OS of patients in RPA class 2 was significantly better than in class 3 ($p < 0.01$; median OS 3.0 vs. 0.7 months). The Barthel Index before treatment was also associated with survival. Patients with an index of 90–100 had a significantly better OS than patients with a score of < 90 ($p = 0.021$; median OS 2.8 vs. 1.6 months).

From a total of 46 patients, 44 completely filled in baseline QoL questionnaires (version A/EORTC QLQ-C30: 11/12 patients; version B/EORTC QLQ-C15-PAL: 34/34 patients; brain module BN20: 44/46 patients). Baseline assessment by proxies was complete in 43 of 46 patients (version A/POS: 10/12; version B/DEGRO-LQ brain module: 33/34). 3 months after radiotherapy, the rate of return of questionnaires of survivors was 17 of 20 (85%). Five patients completed forms of version A and twelve patients of version B. For the newly developed DEGRO-LQ brain module for the assessment by proxies, Cronbach's α was determined to be 0.84, suggesting sufficient reliability to assess brain-specific QoL with this instrument.

Self-assessed QoL was compared for the time points before and 3 months after start of radiotherapy, including only data from patients who completed questionnaires at both time points. Data from EORTC QLQ-C30 and QLQ-C15-PAL were pooled for those domains contained in both question-



naires. Whereas global QoL remained rather stable, physical function deteriorated significantly during the 3 months after start of treatment (Figure 1a; $p < 0.05$, Mann-Whitney U-test). The symptom scales of the above instruments showed a similar downward drift with significant worsening on the scales of fatigue and appetite loss (Figure 1b). In the organ-specific BN20 module, a significant deterioration in drowsiness, hair loss and weakness of legs was noted, whereas the scores for headaches and seizures were slightly better after 3 months (Figure 1c).

In the subgroup in which QoL assessment by proxies was achieved using the POS instrument (version A), the mean score was slightly worse after 3 months (17.8) compared to baseline (15) on a scale from 0 to 40 (40 = maximum impairment; difference not significant). In the other subgroup (version B) evaluated with the brain-specific DEGRO-LQ module, a significantly worse total score was observed at 3 months compared to baseline (Figure 2).

Pretreatment QoL scores of global QoL, emotional and physical function from EORTC QLQ-C30 or QLQ-C15-PAL (scale 0–100, higher score better) differed between patients alive versus deceased at 3 months after start of radiotherapy. The baseline scores for physical function were significantly better in 3-month

Figures 1a to 1c. Self-assessed quality of life (QoL) before and 3 months after start of radiotherapy (RT), presented only for patients for whom data were available at both time points: a) function and global QoL scales from EORTC QLQ-C30 or QLQ-C15-PAL (scale 0–100, higher score better), b) symptom scales from EORTC QLQ-C30 or QLQ-C15-PAL (scale 0–100, higher score worse), c) domains and single items from the brain-specific module EORTC BN20 (higher score worse; *$p < 0.05$, Mann-Whitney U-test).

Abbildungen 1a bis 1c. Lebensqualität (LQ; Selbsteinschätzung) vor und 3 Monate nach Beginn der Strahlentherapie (RT), dargestellt nur für die Patienten, von denen die Daten zu beiden Zeitpunkten erhoben werden konnten: a) Funktions- und globale LQ-Skalen der EORTC-QLQ-C30- oder -QLQ-C15-PAL-Bögen (Skala 0–100, höherer Score besser), b) Symptomskalen der EORTC-QLQ-C30- oder -QLQ-C15-PAL-Bögen (Skala 0–100, höherer Score schlechter), c) Domänen und Einzelitems des hirnspezifischen Moduls EORTC BN20 (höherer Score schlechter; *$p < 0{,}05$, Mann-Whitney-U-Test).

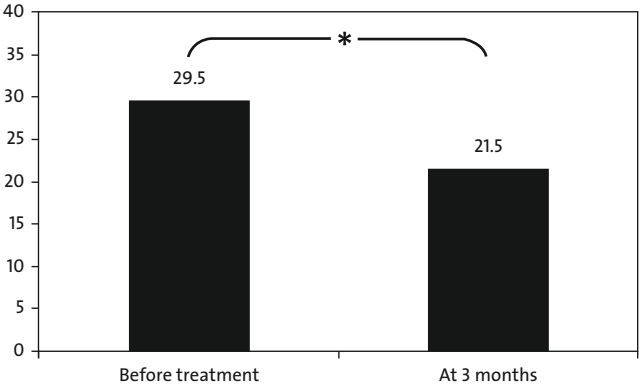


Figure 2. Assessment of quality of life (QoL) by proxies before and 3 months after start of radiotherapy, using the DEGRO-LQ brain module, presented only for patients for whom data were available for both time points (range 0–40, maximum of 40 representing optimal QoL; *p < 0.05, Mann-Whitney-U-test).

Abbildung 2. Erhebung der Lebensqualität (LQ) durch Angehörige vor und 3 Monate nach Beginn der Strahlentherapie unter Verwendung des DEGRO-L Q-Hirnmoduls, dargestellt nur für die Patienten, von denen die Daten zu beiden Zeitpunkten erhoben werden konnten (Range 0–40, Maximum von 40 entspricht einer optimalen LQ; *p < 0,05, Mann-Whitney-U-Test).

survivors than in nonsurvivors (Figure 3a). Similarly, 3-month survivors exhibited significantly better pretreatment scores for the symptom scales of fatigue and pain (Figure 3b) and for the following domains of the BN20 module: motor dysfunction, communication deficit, and weakness of legs (Figure 3c).

To investigate if any brain-specific QoL domain can provide particular prognostic information, we performed OS analyses on subgroups of patients split at the median score for these domains. For the two domains motor dysfunction (median score 1.7; p = 0.091; median OS 3.2 vs. 2.7 months) and communication deficit (median score 1.3; p = 0.073; median OS 3.1 vs. 2.4 months) and the single item weakness of legs (median score 2; p = 0.081; median OS 2.8 vs. 2.7 months), favorable OS was observed in the subgroups with the respective better baseline scores, suggesting that these scores may contain prognostic information.

Discussion

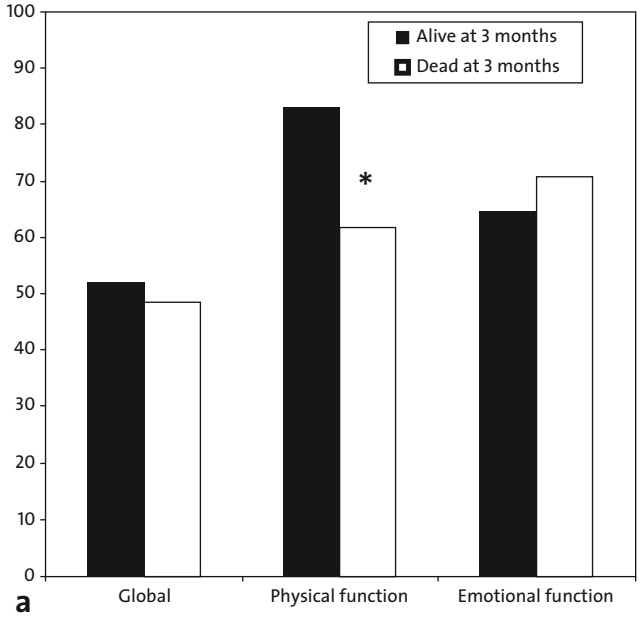
In this pilot phase of a prospective QoL study, the use of the shortened questionnaire variant EORTC QLQ-C15 was most accepted by centers and has been adopted for the ongoing larger-scale study (Figure 4). The assessment of QoL by presenting a brain-specific questionnaire to proxies of the patient was feasible and the ten-item DEGRO-LQ module developed for this purpose showed high reliability. In a simple study design, reducing the burden of repeated questionnaire completion for the incurable patients and of intensive documentation for the centers, QoL was evaluated at only two time points: before treatment and 3 months after initiation of radiotherapy. The second time point was chosen to eliminate the effects of rapid deterioration by very early tumor progression while maintaining a reasonable number of patients available for assessment. The comparison of QoL at the two time points was performed using only data from patients completing questionnaires at both baseline and 3 months, eliminating a potential bias originating from the death of poor-QoL patients [22]. In this pilot phase, less than half of the registered patients were alive at 3 months and thereby assessable for QoL time course.

Few data of QoL of patients with brain metastases already exist in the literature. None of them applied the EORTC QLQ-C15 and brain module BN20. Two studies collected data from patients with WBRT alone and used Functional Assessment of Cancer Therapy questionnaires [3, 7]. At 2 months after WBRT, there was a trend toward worsening general and brain-specific QoL scores like in our study after 3 months. However, there was poor concordance between patients and their proxies for all QoL domains at baseline [7].

An additional aspect is the WBRT-induced tumor shrinkage, which correlates with better survival and neurocognitive function (NCF) preservation. Tumor progression adversely affects NCF more than WBRT does, thus making enhancement of radiation response a worthwhile aim in this patient population [14].

Tumor progression both intra- and extracranially may influence QoL after radiotherapy of brain metastases, as suggested by a small study of patients undergoing stereotactic radiosurgery (SRS) [6]. Patients with no evidence of tumor progression had either unchanged or improved Spitzer Quality of Life Index (SQLI) scores. Respectively, in patients, who failed to respond to treatment in the brain or had an extracranial tumor progression, SQLI scores decreased. These data suggest that achieving local control of brain metastases may be a prerequisite for stabilizing QoL.

The pilot phase now reported has some limitations. The number of patients, especially those available for QoL evaluation at the 3-month time point, is limited despite a high response rate in these severely ill patients. Specific effects in subgroups of patients (e.g., by RPA group or number of metastases) may only be detectable in a much larger overall cohort. Favorable-risk patients such as those suitable for SRS are underrepresented in the present dataset. Therefore, the role of obtaining local control of brain metastases in maintaining or improving QoL could not be assessed in this study. Any effects observed in this study can be attributed to either consequences of intracranial progression, sequelae of brain radiotherapy or (for the non-brain-specific domains) extracranial tumor progression. It will be important in the main phase of this study to analyze the results of posttreatment imaging to differentiate between tumor- and treatment-related QoL effects. Studying additional time points would offer a more complete view of the problem, but it appears questionable whether this would aid in differentiation between tumor- and treatment-related QoL changes. On the basis of the cited work on QoL and NCF in relation to local control, one would speculate that the domi-



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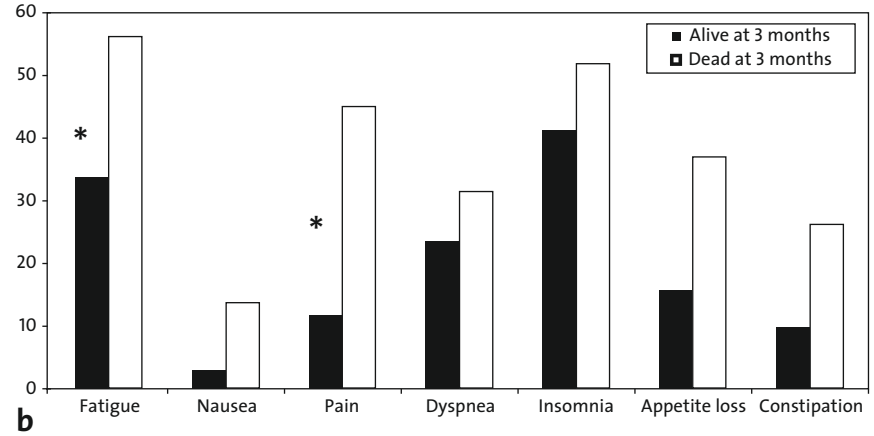

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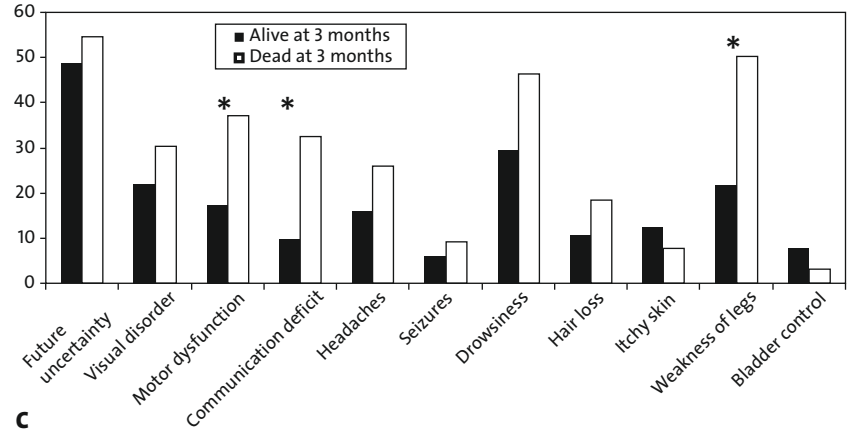

c

nant cause of the QoL deterioration now observed was some form of tumor progression in this poor-prognosis patient group.

The ongoing main phase of the study will determine significant QoL differences over time in a larger patient cohort and may identify significant prognostic effects of QoL domains on survival. Additionally, the effect of different radiotherapy concepts on QoL will be of interest.

Conclusion

Practicability and compliance appeared better with the (shorter) version B. This version is now used in the ongoing main phase of the study which has been expanded to additional centers. Whereas global QoL remained rather stable, physical function deteriorated significantly during the 3 months after start of treatment, also seen at QoL assessed by proxies. QoL at initiation of radiotherapy may be prognostic for survival.

Figures 3a to 3c. Differences in pretreatment quality of life (QoL) between patients alive versus deceased at 3 months after start of radiotherapy: a) function and global QoL scales from EORTC QLQ-C30 or QLQ-C15-PAL (scale 0–100, higher score better), b) symptom scales from EORTC QLQ-C30 or QLQ-C15-PAL (scale 0–100, higher score worse), c) domains and single items from the brain-specific module EORTC BN20 (higher score worse; *p < 0.05, Mann-Whitney U-test).

Abbildungen 3a bis 3c. Differenzen in der Lebensqualität (LQ) vor der Behandlung zwischen den 3-Monats-Überlebenden und den Patienten, die 3 Monate nach Beginn der Radiotherapie bereits verstorben waren: a) Funktions- und globale LQ-Skalen der EORTC-QLQ-C30- oder -QLQ-C15-PAL-Bögen (Skala 0–100, höherer Score besser), b) Symptomskala der EORTC-QLQ-C30- oder -QLQ-C15-PAL-Bögen (Skala 0–100, höherer Score schlechter), c) Domänen und Einzelitems des hirnspezifischen Moduls EORTC BN20 (höherer Score schlechter; *p < 0,05, Mann-Whitney-U-Test).

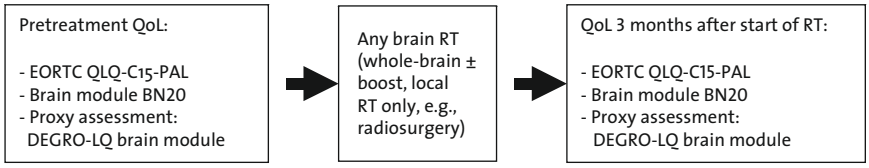

Figure 4. Design of the currently ongoing main phase of the DEGRO-LQ study in patients with brain metastases.

Abbildung 4. Skizzierung der gegenwärtig laufenden Hauptphase der DEGRO-LQ-Studie bei Patienten mit Hirnmetastasen.

Appendix 1: DEGRO-LQ Brain Module for Assessment of Quality of Life by Proxies (Developed by C. Schäfer)

1. How would you rate the general condition of your ill relative?

Very poor	Poor	Intermediate	Good	Very good
0	+1	+2	+3	+4

2. How much has your ill relative been bothered by headaches?

Very much	A lot	Intermediate	A little	Very little
0	+1	+2	+3	+4

3. How much has your ill relative been bothered by nausea?

Very much	A lot	Intermediate	A little	Very little
0	+1	+2	+3	+4

4. How much has your ill relative been bothered by fatigue?

Very much	A lot	Intermediate	A little	Very little
0	+1	+2	+3	+4

5. Has your ill relative been interested in participating in the lives of others?

Very little	A little	Intermediate	A lot	Very much
0	+1	+2	+3	+4

6. Has your ill relative been interested in taking over tasks for others ?

Very little	A little	Intermediate	A lot	Very much
0	+1	+2	+3	+4

7. How satisfied has your ill relative been?

Very little	A little	Intermediate	A lot	Very much
0	+1	+2	+3	+4

8. How balanced has your ill relative been?

Very little	A little	Intermediate	A lot	Very much
0	+1	+2	+3	+4

9. How would you rate the attention of your ill relative in everyday life?

Very little	A little	Intermediate	A lot	Very much
0	+1	+2	+3	+4

10. How would you rate the ability of your ill relative to participate in a longer conversation?

Very poor	Poor	Intermediate	Good	Very good
0	+1	+2	+3	+4

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