

Pre-treatment Emotional Distress in Patients Irradiated for Malignant Glioma

DIRK RADES¹, AHMED AL-SALLOOL¹, NATHAN Y. YU²,
PETER TRILLENBERG³, MATTEO M. BON SANTO⁴ and JAN LEPPERT⁴

¹Department of Radiation Oncology, University of Lübeck, Lübeck, Germany;

²Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ, U.S.A.;

³Department of Neurology, University of Lübeck, Lübeck, Germany;

⁴Department of Neurosurgery, University of Lübeck, Lübeck, Germany

Abstract. *Background/Aim:* A recommendation of radiotherapy for patients with malignant gliomas may trigger emotional distress. Frequency and risk factors of this complication were investigated. *Patients and Methods:* Prevalence of six emotional problems and 11 potential risk factors were evaluated in 103 patients irradiated for grade II-IV gliomas. *p*-Values <0.0045 were considered significant. *Results:* Seventy-six patients (74%) had ≥ 1 emotional problem. Prevalence of specific emotional problems ranged between 23% and 63%. Associations were found between ≥ 5 physical problems and worry ($p=0.0010$), fear ($p=0.0001$), sadness ($p=0.0023$), depression ($p=0.0006$), and loss of interest ($p=0.0006$), and Karnofsky performance score ≤ 80 and depression ($p=0.0002$). Trends were found for physical problems and nervousness ($p=0.040$), age ≥ 60 years and depression ($p=0.043$) or loss of interest ($p=0.045$), grade IV glioma and sadness ($p=0.042$), and ≥ 2 involved sites and loss of interest ($p=0.022$). *Conclusion:* Three-fourths of glioma patients had pre-radiotherapy emotional distress. Psychological support should be offered very soon, particularly for high-risk patients.

Diagnosis and treatment of malignant gliomas often lead to significant distress (1). Distress may be more pronounced if the patients are assigned to radiation therapy. Radiotherapy

Correspondence to: Prof. Dirk Rades, MD, FASTRO, Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23562 Lübeck, Germany. Tel: +49 45150045401, Fax: +49 45150045404, e-mail: dirk.rades@uksh.de

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alone or in combination with chemotherapy is an integral part of the treatment for many glioma patients (2-5). Recommended radiation therapy may cause worry and fear regarding “unnecessary” radiation exposure, unknown technology, or potential adverse events (6-8). Patients may require early psycho-oncologic support to be able to sufficiently tolerate and complete the recommended treatment. In the literature, the prevalence of emotional or psychological distress varies considerably for patients with gliomas (6-61%) (1, 9-15). In our previous study, 67% of patients scheduled for radiotherapy of a malignant glioma reported sleep disorders prior to the start of their treatment, which may be correlated with emotional distress (16). However, there is little data focusing particularly on emotional distress prior to a course of radiotherapy or chemoradiation. Our study evaluates the frequency of six emotional problems and potential risk factors in patients with gliomas of WHO (World Health Organization) grades II, III, or IV, who were recommended for radiotherapy with or without chemotherapy.

Patients and Methods

The data of 103 patients assigned to radiotherapy with or without chemotherapy for a WHO grade II-IV glioma between January 2018 and March 2022 were analyzed regarding emotional distress prior to their course of treatment (17, 18). Emotional distress was assessed according to the National Comprehensive Cancer Network (NCCN) Distress Thermometer and represented by six qualities including worry, fear, sadness, depression, nervousness, and loss of interest in usual activities (19). The study was approved by the local Ethics Committee at the University of Lübeck, Germany (identifier 2022-412).

The patients were irradiated using modern 3D treatment planning and volumetric-modulated arc therapy. Thirteen patients (12.6%) had a WHO grade II glioma, 10 patients (9.7%) a WHO grade III lesion, and 77 patients (74.8%) a WHO grade IV lesion (glioblastoma multiforme). In three patients (2.9%), the WHO grade was not specified. Of the 13 patients with a WHO grade II glioma,



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11 patients received 54.0 Gy (5×1.8 Gy per week), and two patients 59.4 Gy (5×1.8 Gy per week). Eight patients were treated with upfront resection, and five patients received sequential (n=4) or concurrent (n=1) chemotherapy. Of the 10 patients with a WHO grade III glioma, four patients received 59.4 Gy (5×1.8 Gy per week), three patients 60.0 Gy (5×2.0 Gy per week), two patients 55.8 Gy (5×1.8 Gy per week), and one patient 30.4 of planned 59.4 Gy. Eight patients received upfront resection, and all patients chemoradiation, either sequential (n=9) or concurrent (n=1). Of the 77 patients with a WHO grade IV glioma, 58 patients (75%) were treated with 59.4 Gy (5×1.8 Gy per week), five patients with 60.0 Gy (5×2.0 Gy per week), five patients 55.8-57.6 Gy (5×1.8 Gy per week), and nine patients with other dose-fractionation regimens. Upfront resection was performed in 61 patients (79%), and chemoradiation with temozolomide in 70 patients (91%) (20).

Eleven potential risk factors of emotional distress were analyzed including Coronavirus Disease 2019 (COVID-19) pandemic (before vs. during the pandemic), number of physical problems (0-4 vs. ≥5), age (≤59 vs. ≥60 years), sex (female vs. male), Karnofsky performance score (KPS ≤80 vs. >80), number of cerebral sites involved by glioma (1 vs. ≥2 sites), WHO grade (II-III vs. IV), upfront resection (no vs. yes), chemoradiation (no vs. yes), treatment with dexamethasone corticosteroids at the time of assessment of pre-radiotherapy emotional distress (no vs. yes), and history of another malignancy (no vs. yes).

For statistical analyses, we used the Chi-square test or, if the number of patients was n<5 in one or more subgroups, the Fisher's exact test. Following the Bonferroni adjustment for multiple tests, a *p*-value <0.0045 was regarded significant (alpha level of <0.05). In addition, *p*<0.05 were considered to indicate a trend.

Results

Seventy-six patients (74%) showed at least one of the six investigated emotional problems. Prevalence of the emotional problems worry, fear, sadness, depression, nervousness, and loss of interest in usual activities was 53%, 63%, 49%, 21%, 40% and 23%, respectively. Significant associations were found between ≥5 physical problems and worry (*p*=0.0010), fear (*p*=0.0001), sadness (*p*=0.0023), depression (*p*=0.0006), and loss of interest in usual activities (*p*=0.0006), and between a KPS ≤80 and depression (*p*=0.0002). Moreover, trends were found for ≥5 physical problems and nervousness (*p*=0.040), age ≥60 years and depression (*p*=0.043) or loss of interest (*p*=0.045), grade IV glioma and sadness (*p*=0.042), and for ≥2 sites involved by glioma and loss of interest (*p*=0.022). All the results of the associations between the 11 potential risk factors and the six qualities of emotional distress are given in Table I, Table II, Table III, Table IV, Table V, and Table VI.

Discussion

Diagnosis and treatment of malignant brain tumors can lead to significant emotional and psychological distress. In the literature, emotional distress is often represented by anxiety and depression, or by the six qualities included in the NCCN

Distress Thermometer, namely worry, fear, sadness, depression, nervousness, and loss of interest in usual activities (19). The prevalence of emotional distress shows considerable variations, depending on the patients' situation. In a prospective observational study of 149 patients with low-grade glioma, an increased level of distress was found in 20.8% of these patients (9). In a pilot study including 32 patients with high-grade glioma and 31 caregivers, 19 of the patients (60%) reported clinically significant distress (10). In another study considering both patients and caregivers, 37.5% of the patients with a primary brain tumor had distress scores above the cut-off value at the time of diagnoses (12). The study of Randazzo *et al.* used the NCCN Distress Thermometer to evaluate psychosocial distress in a series of 829 patients with a primary brain tumor (11, 19). The prevalence of worry, fear, and nervousness was 29.4%, 17.5%, and 22.4%, respectively. In the study of Mainio *et al.*, 35% of the patients reported depression prior to resection of a primary brain tumor (15). Rooney *et al.* assessed five qualities of emotional distress using the Distress Thermometer at different time points (13). At the earliest time point, *i.e.*, shortly after the start of radiotherapy or chemotherapy, worry, fear, sadness, depression, and nervousness were stated by 29%, 14%, 15%, 6%, and 19%, respectively. Moreover, in a systematic review that considered 92 articles, a prevalence of 60.9% was found for mental health disorders (1). No study so far focused specifically on the prevalence of emotional distress prior to radiotherapy or chemoradiation for malignant gliomas. In our study addressing this situation, 74% of the patients indicated at least one emotional problem. Moreover, the prevalence of the six investigated qualities of emotional distress was higher than that in the studies of Randazzo *et al.* and Rooney *et al.* (11, 13). These results support the hypothesis that upcoming radiotherapy is particularly stressful for glioma patients.

In our study, emotional distress was significantly associated with a greater number of physical problems and a lower KPS. In addition, trends were found for older age (≥60 years), glioblastoma multiforme, and involvement of ≥2 cerebral sites. The prognostic role of physical problems was previously described in other studies. In the study of Osoba *et al.*, deteriorating neurologic status was associated with increase in emotional distress in patients with brain tumors (21). Halkett *et al.* found that poor physical function was related to multiple domains of distress in a cohort of 116 patients with high-grade gliomas (22). In the study of Aprile *et al.*, mental aspects of quality of life were significantly related to fatigue, which is one of the physical problems addressed in the NCCN Distress Thermometer (19, 23). Moreover, in our preceding study, the number of physical problems were positively correlated with sleep disorders that might have been a consequence of emotional distress (13). Associations between a worse KPS and a higher prevalence

Table I. Associations of the investigated characteristics and worry.

Characteristic		Worry, n (%)		p-Value
		Yes	No	
COVID-19 pandemic	Before (n=59)	31 (53)	28 (47)	0.84
	During (n=44)	24 (55)	20 (45)	
Number of physical problems	0-4 (n=53)	20 (38)	33 (62)	0.0010
	≥5 (n=50)	35 (70)	15 (30)	
Age	≤59 Years (n=57)	32 (56)	25 (44)	0.53
	≥60 Years (n=46)	23 (50)	23 (50)	
Sex	Female (n=45)	25 (56)	20 (44)	0.70
	Male (n=58)	30 (52)	28 (48)	
Karnofsky performance score	≤80 (n=48)	27 (56)	21 (44)	0.59
	>80 (n=55)	28 (51)	27 (49)	
Number of involved sites	1 (n=71)	40 (56)	31 (44)	0.37
	≥2 (n=32)	15 (47)	17 (53)	
WHO grade*	II-III (n=23)	13 (57)	10 (43)	0.87
	IV (n=77)	42 (55)	35 (45)	
Upfront resection	No (n=25)	16 (64)	9 (36)	0.22
	Yes (n=78)	39 (50)	39 (50)	
Chemoradiation	No (n=18)	9 (50)	9 (50)	0.75
	Yes (n=85)	46 (54)	39 (46)	
Dexamethasone [#]	No (n=36)	18 (50)	18 (50)	0.66
	Yes (n=66)	36 (55)	30 (45)	
History of another malignancy [#]	No (n=84)	44 (52)	40 (48)	0.81
	Yes (n=18)	10 (56)	8 (44)	

COVID-19: Coronavirus Disease 2019; WHO: World Health Organization; *unknown in 3 patients; [#]unknown in 1 patient. Following Bonferroni adjustment, *p*-values <0.0045 are significant and given in bold.

Table II. Associations of the investigated characteristics and fear.

Characteristic		Fear, n (%)		p-Value
		Yes	No	
COVID-19 pandemic	Before (n=59)	36 (61)	23 (39)	0.61
	During (n=44)	29 (66)	15 (34)	
Number of physical problems	0-4 (n=53)	24 (45)	29 (55)	0.0001
	≥5 (n=50)	41 (82)	9 (18)	
Age	≤59 Years (n=57)	36 (63)	21 (37)	0.99
	≥60 Years (n=46)	29 (63)	17 (37)	
Sex	Female (n=45)	30 (67)	15 (33)	0.51
	Male (n=58)	35 (60)	23 (40)	
Karnofsky performance score	≤80 (n=48)	32 (67)	16 (33)	0.48
	>80 (n=55)	33 (60)	22 (40)	
Number of involved sites	1 (n=71)	43 (61)	28 (39)	0.43
	≥2 (n=32)	22 (69)	10 (31)	
WHO grade*	II-III (n=23)	14 (61)	9 (39)	0.72
	IV (n=77)	50 (65)	27 (35)	
Upfront resection	No (n=25)	19 (76)	6 (24)	0.12
	Yes (n=78)	46 (59)	32 (41)	
Chemoradiation	No (n=18)	12 (67)	6 (33)	0.73
	Yes (n=85)	53 (62)	32 (38)	
Dexamethasone [#]	No (n=36)	23 (64)	13 (36)	0.86
	Yes (n=66)	41 (62)	25 (38)	
History of another malignancy [#]	No (n=84)	53 (63)	31 (37)	0.87
	Yes (n=18)	11 (61)	7 (39)	

COVID-19: Coronavirus Disease 2019; WHO: World Health Organization; *unknown in 3 patients; [#]unknown in 1 patient. Following Bonferroni adjustment, *p*-values <0.0045 are significant and given in bold.

Table III. Associations of the investigated characteristics and sadness.

Characteristic		Sadness, n (%)		p-Value
		Yes	No	
COVID-19 pandemic	Before (n=59)	28 (47)	31 (53)	0.80
	During (n=44)	22 (50)	22 (50)	
Number of physical problems	0-4 (n=53)	18 (34)	35 (66)	0.0023
	≥5 (n=50)	32 (64)	18 (36)	
Age	≤59 Years (n=57)	27 (47)	30 (53)	0.79
	≥60 Years (n=46)	23 (50)	23 (50)	
Sex	Female (n=45)	20 (44)	25 (56)	0.46
	Male (n=58)	30 (52)	28 (48)	
Karnofsky performance score	≤80 (n=48)	28 (58)	20 (42)	0.063
	>80 (n=55)	22 (40)	33 (60)	
Number of involved sites	1 (n=71)	37 (52)	34 (48)	0.28
	≥2 (n=32)	13 (41)	19 (59)	
WHO grade*	II-III (n=23)	7 (30)	16 (70)	0.042
	IV (n=77)	42 (55)	35 (45)	
Upfront resection	No (n=25)	13 (52)	12 (48)	0.69
	Yes (n=78)	37 (47)	41 (53)	
Chemoradiation	No (n=18)	8 (44)	10 (56)	0.79
	Yes (n=85)	42 (49)	43 (51)	
Dexamethasone [#]	No (n=36)	15 (42)	21 (58)	0.34
	Yes (n=66)	34 (52)	32 (48)	
History of another malignancy [#]	No (n=84)	40 (48)	44 (52)	0.85
	Yes (n=18)	9 (50)	9 (50)	

COVID-19: Coronavirus Disease 2019; WHO: World Health Organization; *unknown in 3 patients; [#]unknown in 1 patient. Following Bonferroni adjustment, *p*-values <0.0045 are significant and given in bold.

Table IV. Associations of the investigated characteristics and depression.

Characteristic		Depression, n (%)		p-Value
		Yes	No	
COVID-19 pandemic	Before (n=59)	11 (19)	48 (81)	0.44
	During (n=44)	11 (25)	33 (75)	
Number of physical problems	0-4 (n=53)	4 (8)	49 (92)	0.0006
	≥5 (n=50)	18 (36)	32 (64)	
Age	≤59 Years (n=57)	8 (14)	49 (86)	0.043
	≥60 Years (n=46)	14 (30)	32 (70)	
Sex	Female (n=45)	12 (27)	33 (73)	0.25
	Male (n=58)	10 (17)	48 (83)	
Karnofsky performance score	≤80 (n=48)	18 (38)	30 (63)	0.0002
	>80 (n=55)	4 (7)	51 (93)	
Number of involved sites	1 (n=71)	16 (23)	55 (77)	0.66
	≥2 (n=32)	6 (19)	26 (81)	
WHO grade*	II-III (n=23)	5 (22)	18 (78)	0.92
	IV (n=77)	16 (21)	61 (79)	
Upfront resection	No (n=25)	7 (28)	18 (72)	0.35
	Yes (n=78)	15 (19)	63 (81)	
Chemoradiation	No (n=18)	2 (11)	16 (89)	0.35
	Yes (n=85)	20 (24)	65 (76)	
Dexamethasone [#]	No (n=36)	5 (14)	31 (86)	0.22
	Yes (n=66)	16 (24)	50 (76)	
History of another malignancy [#]	No (n=84)	18 (21)	66 (79)	0.76
	Yes (n=18)	3 (17)	15 (83)	

COVID-19: Coronavirus Disease 2019; WHO: World Health Organization; *unknown in 3 patients; [#]unknown in 1 patient. Following Bonferroni adjustment, *p*-values <0.0045 are significant and given in bold.

Table V. Associations of the investigated characteristics and nervousness.

Characteristic		Nervousness, n (%)		p-Value
		Yes	No	
COVID-19 pandemic	Before (n=59)	23 (39)	36 (61)	0.84
	During (n=44)	18 (41)	26 (59)	
Number of physical problems	0-4 (n=53)	16 (30)	37 (70)	0.040
	≥5 (n=50)	25 (50)	25 (50)	
Age	≤59 Years (n=57)	23 (40)	34 (60)	0.90
	≥60 Years (n=46)	18 (39)	28 (61)	
Sex	Female (n=45)	18 (40)	27 (60)	0.97
	Male (n=58)	23 (40)	35 (60)	
Karnofsky performance score	≤80 (n=48)	19 (40)	29 (60)	0.97
	>80 (n=55)	22 (40)	33 (60)	
Number of involved sites	1 (n=71)	27 (38)	44 (62)	0.58
	≥2 (n=32)	14 (44)	18 (56)	
WHO grade*	II-III (n=23)	9 (39)	14 (61)	0.99
	IV (n=77)	30 (39)	47 (61)	
Upfront resection	No (n=25)	11 (44)	14 (56)	0.62
	Yes (n=78)	30 (38)	48 (62)	
Chemoradiation	No (n=18)	9 (50)	9 (50)	0.33
	Yes (n=85)	32 (38)	53 (62)	
Dexamethasone [#]	No (n=36)	10 (28)	26 (72)	0.059
	Yes (n=66)	31 (47)	35 (53)	
History of another malignancy [#]	No (n=84)	33 (39)	51 (61)	0.69
	Yes (n=18)	8 (44)	10 (56)	

COVID-19: Coronavirus Disease 2019; WHO: World Health Organization; *unknown in 3 patients; [#]unknown in 1 patient. Following Bonferroni adjustment, *p*-values <0.0045 are significant.

Table VI. Associations of the investigated characteristics and loss of interest in usual activities.

Characteristic		Loss of interest in usual activities, n (%)		p-Value
		Yes	No	
COVID-19 pandemic	Before (n=59)	12 (20)	47 (80)	0.41
	During (n=44)	12 (27)	32 (73)	
Number of physical problems	0-4 (n=53)	5 (9)	48 (91)	0.0006
	≥5 (n=50)	19 (38)	31 (62)	
Age	≤59 Years (n=57)	9 (16)	48 (84)	0.045
	≥60 Years (n=46)	15 (33)	31 (67)	
Sex	Female (n=45)	10 (22)	35 (78)	0.82
	Male (n=58)	14 (24)	44 (76)	
Karnofsky performance score	≤80 (n=48)	15 (31)	33 (69)	0.075
	>80 (n=55)	9 (16)	46 (84)	
Number of involved sites	1 (n=71)	12 (17)	59 (83)	0.022
	≥2 (n=32)	12 (38)	20 (63)	
WHO grade*	II-III (n=23)	5 (22)	18 (78)	0.87
	IV (n=77)	18 (23)	59 (77)	
Upfront resection	No (n=25)	7 (28)	18 (72)	0.52
	Yes (n=78)	17 (22)	61 (78)	
Chemoradiation	No (n=18)	4 (22)	14 (78)	>0.99
	Yes (n=85)	20 (24)	65 (76)	
Dexamethasone [#]	No (n=36)	5 (14)	31 (86)	0.090
	Yes (n=66)	19 (29)	47 (71)	
History of another malignancy [#]	No (n=84)	22 (26)	62 (74)	0.23
	Yes (n=18)	2 (11)	16 (89)	

COVID-19: Coronavirus Disease 2019; WHO: World Health Organization; *unknown in 3 patients; [#]unknown in 1 patient. Following Bonferroni adjustment, *p*-values <0.0045 are significant and given in bold.

of distress was previously reported by Mainio *et al.* (15). In addition, Rooney *et al.* found a significant association between KPS ≤ 70 and depressive disorders shortly after the start of radiotherapy for cerebral glioma (14). In the study of Abete-Fornara *et al.*, the probability to experience severe psychological distress was significantly associated with older age (odds ratio=1.17, $p=0.0004$) in patients with brain tumors (24). The fact that distress was correlated with more aggressive gliomas (higher WHO grades) was shown by Trad *et al.* (distress assessed at the time of diagnosis) and Leonetti *et al.* (distress assessed 6 months following resection) (12, 25). An association between emotional distress and involvement of ≥ 2 cerebral sites was not explicitly stated before. However, since this situation is associated with a significantly worse survival prognosis than a single lesion, one can understand that affected patients experience a higher level of distress (5).

In conclusion, approximately 75% of patients with a malignant glioma reported at least one aspect of emotional distress prior to their course of radiotherapy or chemoradiation. High-risk patients, namely those with ≥ 5 physical problems, KPS ≤ 80 , age ≥ 60 years, glioblastoma multiforme, or involvement of ≥ 2 cerebral sites should be offered psychological support very soon.

Conflicts of Interest

The Authors report no conflicts of interest in relation to this study.

Authors' Contributions

All Authors participated in the study design. A. A.-L. and D.R. collected the data. Data analysis was performed by D.R. The article was drafted by D.R. and N.Y.Y.; it was reviewed and approved by all Authors.

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