

Risk Factors for Sleep Problems Prior to Radiochemotherapy for Malignant Gliomas

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Abstract. *Background/Aim: Many patients with malignant gliomas are scheduled for radiochemotherapy, which may cause emotional distress associated with sleep problems. This study aimed to determine the prevalence of such sleep problems in these patients and identify risk factors. Patients and Methods: Fifty-seven patients scheduled for radiochemotherapy for grade II-IV gliomas were retrospectively investigated for pre-treatment sleep problems. Fifteen characteristics were evaluated including temporal relation to COVID-19 pandemic, age, gender, performance status, comorbidity, (family) history of malignancies, distress score, emotional problems, physical problems, practical problems, involved sites, glioma grade, upfront surgery, and corticosteroids. Results: Nineteen patients stated pre-treatment sleep problems (prevalence=66.7%). Significant associations with sleep problems were found for female gender ($p=0.023$), presence of emotional problems ($p=0.006$), and ≥ 4 physical problems ($p<0.001$). A trend was found for distress scores ≥ 5 ($p=0.077$). Conclusion: The prevalence of sleep problems was high. Risk factors were determined that can be used to identify patients who likely benefit from psychological support.*

According to the classification of the World Health Organization (WHO), the group of gliomas includes four

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grades (grades I to IV), of which grade IV tumors (glioblastoma multiforme) are the most aggressive lesions with a 5-year survival rate of about 5% (1-3).

Neurosurgical resection should be performed whenever safely possible. In patients with grade III or IV gliomas, resection is generally followed by radiochemotherapy (4-6). This applies also to selected patients with grade II gliomas, mainly after incomplete resection. Assignment to a course of radiochemotherapy may cause significant distress for the patients who may be afraid particularly of the exposure to radiation and potential treatment-related adverse events (7-10). The distress may lead to sleep problems that can significantly impair the patients' quality of life and require psychological support already prior to the start of radiochemotherapy (11-13). Therefore, the present study investigated the prevalence and potential risk factors of pre-treatment sleep problems in patients with grade II to IV gliomas assigned to radiochemotherapy. These data can contribute to the identification of patients who would likely benefit from psychological support beginning already prior to their course of radiochemotherapy.

Patients and Methods

In this retrospective study, 57 patients scheduled for radiochemotherapy of WHO grade II-IV gliomas were investigated with respect to pre-treatment sleep problems. These patients had completed the National Comprehensive Cancer Network (NCCN) Distress Thermometer (14, 15) between February 2019 and March 2021. The study was approved as a part of a larger project by the Ethics Committee of the University of Lübeck (reference 21-284). The technique to be used for the planned radiotherapy was volumetric-modulated arc therapy (VMAT). The preferred dose-fractionation regimen for grade III and grade IV gliomas was 59.4 Gy in 33 fractions of 1.8 Gy. In case of involvement of the brain stem, total doses were reduced to 55.8 Gy or 57.8 Gy. For grade II lesions, the preferred regimen was 54.0 Gy in 30 fractions of 1.8 Gy. Finally, three patients did not receive the complete planned dose due to tumor

progression or other complications during the course of radiotherapy. Fifty-four patients (94.7%) of the patients received chemotherapy in addition to their radiation treatment, mostly with temozolomide (16).

Fifteen characteristics (Table I) were investigated for potential associations with the occurrence of pre-treatment sleep problems including temporal relation to the Coronavirus Disease 2019 (COVID-19) pandemic (prior to vs. during the pandemic), age (≤ 58 vs. ≥ 59 years, median age=59 years), gender (female vs. male), Karnofsky performance score (≤ 60 vs. ≥ 70), Charlson comorbidity index (2-4 vs. ≥ 5), history of another malignancy (no vs. yes), family history of malignancy (no vs. yes), distress score (0-4 vs. ≥ 5), emotional problems (no vs. yes), number of physical problems (0-3 vs. ≥ 4), practical problems (no vs. yes), number of involved sites (1 vs. ≥ 2), WHO grade (II-III vs. IV), upfront surgery (no vs. yes), and treatment with corticosteroids at the time of evaluation with the (NCCN) Distress Thermometer (no vs. yes). Emotional, physical and practical problems were assessed with the (NCCN) Distress Thermometer (14, 15). The statistical analyses regarding the associations between the 15 investigated characteristics and occurrence of pre-treatment sleep problems were performed with the Fisher's exact test. *p*-Values of less than 0.05 were considered significant, and *p*-values of less than 0.10 indicated a trend.

Results

Nineteen of the 57 patients stated sleep problems prior to their planned course of radiochemotherapy, corresponding to a prevalence of 66.7%. Significant associations with occurrence of sleep problems were found for female gender ($p=0.023$), presence of emotional problems ($p=0.006$), and ≥ 4 physical problems ($p<0.001$) (Table II). In addition, a trend was found for distress scores ≥ 5 ($p=0.077$). The temporal relation to the COVID-19 pandemic did not show a significant association with pre-treatment sleep problems ($p=0.78$) (Table II).

Discussion

The majority of patients with grade III or IV gliomas and selected patients with grade II gliomas are scheduled for radiochemotherapy, mainly following neurosurgical resection (4-6). This situation may produce significant emotional distress for the patients due to fears regarding the treatment procedure, potential side effects, and unsatisfactory treatment outcomes including progression or recurrence of the glioma (7-10, 17-19). These fears may lead to sleep problems that can significantly impair the patients' quality of life (11-13). Affected patients would likely benefit from near-term psychological support. However, no study could be identified in the literature that focused particularly on sleep problems prior to radiochemotherapy of gliomas.

The present study aimed to contribute to filling this gap to some extent by evaluating the prevalence of pre-treatment sleep problems and potential risk factors in patients with grade II-IV gliomas assigned to radiochemotherapy. The prevalence of pre-treatment sleep disorders was 66.7% and higher than in patients with solid cancers such as breast

Table I. Evaluated patient and tumor characteristics.

Characteristic	Subgroup	Frequency, n (%)
COVID-19 pandemic	Before	33 (58)
	During	24 (42)
Age	≤ 58 Years	29 (51)
	≥ 59 Years	28 (49)
Gender	Female	25 (44)
	Male	32 (56)
Karnofsky performance score	≤ 60	10 (18)
	≥ 70	47 (82)
Charlson comorbidity index	2-4	38 (67)
	≥ 5	19 (33)
History of another malignancy	No	50 (88)
	Yes	6 (11)
	Unknown	1 (2)
Family history of malignancy	No	30 (53)
	Yes	26 (46)
	Unknown	1 (2)
Distress-score	0-4	20 (35)
	≥ 5	37 (65)
Emotional problems	No	16 (28)
	Yes	41 (72)
Number of physical problems	0-3	24 (42)
	≥ 4	33 (58)
Practical problems	No	25 (44)
	Yes	32 (56)
Number of involved sites	1	41 (72)
	≥ 2	16 (28)
WHO Grade	II-III	14 (25)
	IV	43 (75)
Upfront surgery	No	13 (23)
	Yes	44 (77)
Corticosteroids	No	27 (47)
	Yes	29 (51)
	Unknown	1 (2)

COVID-19: Coronavirus Disease 2019; WHO: World Health Organization.

cancer (42.3%), gynecological cancers (46.8%), head-and-neck-cancers (42.7%), and prostate cancer (20.8%) (20-23). Moreover, the prevalence in the current study was higher than in a study of patients with recurrent glial neoplasms (46.8%), in a study evaluating patients with glioma following surgical resection (33.7%), and in a study evaluating sleep problems during the year prior to the diagnosis of adult glioma (41%) (11, 24, 25). However, due to the different settings, it does not appear reasonable to compare these data to the results of our present study.

In addition to the determination of the prevalence of sleep problems prior to radiochemotherapy, the current study aimed to identify risk factors for sleep problems. Significant associations were found between the occurrence of sleep problems and female gender, emotional problems, and physical problems. Moreover, a trend was observed for higher distress scores. Some of these findings agree with the results of a

Table II. Associations between characteristics and pre-treatment sleep problems.

Characteristic		Sleep disorders, n (%)		p-Value
		Yes (n=38)	No (n=19)	
COVID-19 pandemic	Before	21 (55)	12 (63)	0.78
	During	17 (45)	7 (37)	
Age	≤58 Years	18 (47)	11 (58)	0.58
	≥59 Years	20 (53)	8 (42)	
Gender	Female	21 (55)	4 (21)	0.023
	Male	17 (45)	15 (79)	
Karnofsky performance score	≤60	8 (21)	2 (11)	0.47
	≥70	30 (79)	17 (89)	
Charlson comorbidity index	2-4	24 (63)	14 (74)	0.56
	≥5	14 (37)	5 (26)	
History of another malignancy	No	34 (92)	16 (84)	0.40
	Yes	3 (8)	3 (16)	
Family history of malignancy	No	20 (54)	10 (53)	>0.99
	Yes	17 (46)	9 (47)	
Distress-score	0-4	10 (26)	10 (53)	0.077
	≥5	28 (74)	9 (47)	
Emotional problems	No	6 (16)	10 (53)	0.006
	Yes	32 (84)	9 (47)	
Number of physical problems	0-3	9 (24)	15 (79)	<0.001
	≥4	29 (76)	4 (21)	
Practical problems	No	14 (37)	11 (58)	0.16
	Yes	24 (63)	8 (42)	
Number of involved sites	1	28 (74)	13 (68)	0.76
	≥2	10 (26)	6 (32)	
WHO Grade	II-III	9 (24)	5 (26)	>0.99
	IV	29 (76)	14 (74)	
Upfront surgery	No	11 (29)	2 (11)	0.18
	Yes	27 (71)	17 (89)	
Corticosteroids	No	19 (51)	8 (42)	0.58
	Yes	18 (49)	11 (58)	

COVID-19: Coronavirus Disease 2019; WHO: World Health Organization. Significant *p*-values given in bold.

prospective cohort study of adult patients with newly diagnosed glioma receiving active management (26). This study investigated emotional distress and found that sleep problems was one of the most frequently reported causes of distress. Distress scores (14) were comparably high in patients who were functionally impaired (physical problems) and in patients who were depressed (emotional problem) (24). Moreover, in the study investigating insomnia in patients with recurrent glial neoplasms, trends were observed for an association between insomnia and fatigue (physical problem) (11). Associations between higher distress scores and sleep problems prior to radiotherapy or radiochemotherapy were shown for patients with breast cancer, prostate cancer, and rectal or anal cancer (20, 22, 27). A trend for an association between pre-radiotherapy sleep problems and female gender was also reported for patients irradiated for rectal or anal cancer (27). However, since our present study can be considered unique, as it is the first study evaluating sleep problems prior to radiochemotherapy in patients with malignant gliomas, its results may not be directly

compared to studies that included differing tumor types. Moreover, when interpreting, the retrospective study design should be considered.

In conclusion, the prevalence of sleep problems prior to radiochemotherapy for gliomas was high. The risk factors that were determined in this study can be used to identify patients who likely benefit from psychological support offered already prior to the start of treatment.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there are no conflicts of interest related to this study.

Authors' Contributions

S.K., T.W.K., S.T., T.B. and D.R. designed the study; S.K. provided the data that were analyzed by S.E.S. and D.R.; S.K., S.E.S. and D.R. drafted the article, which was reviewed and approved by all Authors.

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