ANTICANCER RESEARCH *41*: 5065-5069 (2021)
doi:10.21873/anticanres.15322

Risk Factors for Sleep Disturbances in Patients Scheduled for Radiotherapy of Head-and-Neck Cancer

DIRK RADES[1], SVENJA KOPELKE[1,2], TAMER SOROR[1], TOBIAS BARTSCHT[2], SOEREN TVILSTED[3], TROELS W. KJAER[4] and STEVEN E. SCHILD[5]

[1]*Department of Radiation Oncology, University of Lübeck, Lübeck, Germany;*
[2]*Department of Hematology and Oncology, University of Lübeck, Lübeck, Germany;*
[3]*Research Projects and Clinical Optimization, Zealand University Hospital, Koege, Denmark;*
[4]*Department of Neurology, Zealand University Hospital, Roskilde, Denmark;*
[5]*Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.*

Abstract. *Background/Aim: Many patients with head-and-neck cancer are scheduled for irradiation. This study was performed to determine the frequency of and risk factors for pre-radiotherapy sleep disturbances in these patients. Patients and Methods: A total of 103 patients with head-and-neck cancer scheduled for radiotherapy were included in this retrospective study. Eighteen characteristics were evaluated including timing of start of radiotherapy relative to COVID-19 pandemic; age; gender; Karnofsky performance score; Charlson comorbidity index; history of another malignancy; family history of malignancy; distress score; number of emotional, physical or practical problems; request for psychological support; tumor site and stage; upfront surgery; planned chemotherapy; and brachytherapy boost. Results: The frequency of pre-radiotherapy sleep disturbances was 42.7%. This was significantly associated with age ≤63 years (p=0.049), Karnofsky performance score ≤80 (p=0.002), Charlson comorbidity index ≥3 (p=0.005), history of another malignancy (p=0.012), emotional (p=0.001) or physical (p<0.001) problems, and request for psychological support (p=0.002). Conclusion: Sleep disturbances were frequent in patients assigned to radiotherapy of head-and-neck cancer. Recognizing risk factors for sleep disturbance helps identify patients requiring psychological support.*

Correspondence to: Professor Dirk Rades, MD, 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

Key Words: Head-and-neck cancer, irradiation, sleep disturbance, frequency, risk factors.

Irradiation with or without concurrent chemotherapy is a common treatment for locally advances head-and-neck cancer, either alone or following surgical resection (1-3). Patients assigned to a course of radiotherapy may be scared due to the upcoming exposure to radiation and potential treatment-related toxicity. This situation may lead to significant emotional distress accompanied by sleep disturbances. According to a study of patients irradiated for breast or prostate cancer, sleep disturbances occurred mainly before or during the first week of the radiotherapy course (4). Data regarding pre-radiotherapy sleep disturbances in patients with head-and-neck cancer are rare. Therefore, the current study was conducted to contribute to the knowledge of sleep disturbances before starting a course of radiotherapy in this particular group of patients. Its major goals included the determination of the frequency of pre-radiotherapy sleep disturbances and identification of risk factors regarding the occurrence of such disturbances. Understanding corresponding risk factors will facilitate the identification of patients with head-and-neck cancer who would likely benefit from psychological support prior to their radiation treatment.

Patients and Methods

A total of 103 patients with locally advanced head-and-neck cancer who were scheduled for radiotherapy or chemoradiation and completed the National Comprehensive Cancer Network Distress Thermometer (5, 6) between March 2019 and February 2021 were included in this retrospective study. The study received approval from the Ethics Committee at the University of Lübeck (reference number: 21-284).

External beam radiotherapy (EBRT) was planned to be performed as volumetric-modulated arc therapy. In 93 patients, a dose of 50 Gy (5×2.0 Gy per week) was planned for the primary tumor and regional lymph nodes, including low-risk areas. In 90 patients, depending on the type of radiotherapy (definitive or adjuvant) and the extent of resection, sequential boost doses were

10 Gy after microscopically complete resection, 14-16 Gy after microscopically incomplete resection/extracapsular extension of lymph node metastasis, and 20 Gy after macroscopically incomplete resection or as definitive treatment. Three of the 93 patients received a brachytherapy boost of 4-5×2.5 Gy after 50 Gy. Of the other 10 patients, two received EBRT with 1.8 Gy per fraction up to 54 Gy and 59.4 Gy (plus 4×2.5 Gy of brachytherapy), respectively; one received EBRT with 50 Gy in 25 fractions plus a simultaneous integrated boost of 0.5 Gy per fraction; and seven patients who could not receive concurrent chemotherapy were irradiated with a concomitant boost regimen including 30 Gy (5×2.0 Gy over 3 weeks) to primary tumor and regional lymph nodes including low-risk areas followed by 21.6 Gy (5×1.8 Gy per week) to the same areas in the morning (cumulative dose=51.6 Gy) plus boost of 1.5 Gy per fraction after an interval of at least 6 hours on the same days to total doses of 60.6 Gy (intermediate-risk lymph node areas) and 69.6 Gy (primary tumor and involved/high-risk lymph node areas), respectively (7-10). Concurrent chemotherapy was planned for 73 patients, either with two courses of cisplatin (20 mg/m^2/d 1-5 or 25 mg/m^2/d 1-4) every 4 weeks (n=48) or two courses of carboplatin (area under the curve of 1.0/d 1-5 or 1.5/d 1-4) every 4 weeks (n=25).

Eighteen patient- and tumor-specific characteristics were evaluated for associations with pre-radiotherapy sleep disturbances. These characteristics included the timing of the start of radiotherapy relative to the COVID-19 pandemic (before *vs*. during the pandemic); age (≤63 *vs*. ≥64 years, median=63 years); gender (female *vs*. male); Karnofsky performance score (KPS ≤80 *vs*. ≥90); Charlson comorbidity index (CCI 2 *vs*. ≥3); patient's history of another malignancy (no *vs*. yes); family history of malignancy (no *vs*. yes); distress score (0-5 *vs*. 6-10); number of emotional (0-1 *vs*. ≥2), physical (0-4 *vs*. ≥5) or practical (0 *vs*. ≥1) problems according to the National Comprehensive Cancer Network Distress Thermometer (5, 6); patient's request for psychological support (no *vs*. yes); tumor site (oropharynx *vs*. oral cavity/floor of mouth *vs*. hypopharynx *vs*. larynx *vs*. other sites); primary tumor stage (T1-2 *vs*. T3-4); nodal stage (N0 *vs*. N+); upfront surgery (no *vs*. yes); planned concurrent chemotherapy (no *vs*. yes); and brachytherapy boost (no *vs*. yes) (Table I). Other sites included the nasopharynx in one, paranasal sinus in seven, and salivary glands in four patients.

For statistical analyses regarding the evaluation of associations between pre-radiotherapy sleep disturbances and the 18 characteristics, the chi-square test or (when n<5) Fisher's exact test. *p*-Values of less than 0.05 were considered statistically significant.

Table I. *Evaluated patient and tumor characteristics.*

Characteristic	Subgroup	Frequency, n (%)
COVID-19 pandemic	Before	52 (50)
	During	51 (50)
Age	≤63 Years	54 (52)
	≥64 Years	49 (48)
Gender	Female	24 (23)
	Male	79 (77)
Karnofsky performance score	≤80	45 (44)
	≥90	58 (56)
Charlson comorbidity index	2	42 (41)
	≥3	61 (59)
History of another malignancy	No	88 (85)
	Yes	15 (15)
Family history of malignancy	No	54 (52)
	Yes	45 (44)
	Unknown	4 (4)
Distress-score	0-5	67 (65)
	6-10	36 (35)
Number of emotional problems	0-1	52 (50)
	≥2	51 (50)
Number of physical problems	0-4	55 (53)
	≥5	48 (47)
Number of practical problems	0	66 (64)
	≥1	37 (36)
Request for psychological support	No	73 (71)
	Yes	30 (29)
Tumor site	Oropharynx	49 (48)
	Oral cavity/FoM	13 (13)
	Hypopharynx	22 (21)
	Larynx	7 (7)
	Other	12 (12)
Primary tumor stage	T1-2	39 (38)
	T3-4	64 (62)
Nodal stage	N0	22 (21)
	N+	81 (79)
Upfront surgery	No	43 (42)
	Yes	60 (58)
Planned concurrent chemotherapy	No	30 (29)
	Yes	73 (71)
Brachytherapy boost	No	98 (95)
	Yes	5 (5)

COVID-19: Coronavirus Disease 2019; FoM: floor of mouth; SCC: squamous cell carcinoma.

Results

The frequency of sleep disturbances prior to the planned course of radiotherapy was 42.7%, *i.e*., in 44 of this cohort of 103 patients. Sleep disturbance was significantly associated with age ≤63 years (p=0.049), KPS ≤80 (p=0.002), CCI ≥3 (p=0.005), patient's history of another malignancy (p=0.012), ≥2 emotional problems (p=0.001), ≥5 physical problems (p<0.001) and patient's request for psychological support (p=0.002).

In contrast, no association with the time of the COVID-19 pandemic was found (p=0.27). The complete results of the analyses are shown in Table II.

Discussion

In patients with head-and-neck cancer scheduled for definitive or adjuvant radiotherapy, concerns about treatment and side-effects may cause significant emotional stress and sleep disturbances (11-15). Detailed knowledge regarding the frequency of sleep disturbances in these patients and risk factors will contribute to a better understanding of this problem. Sleep disturbances significantly impair the patients' quality of life, and the findings from this study can help

Table II. *Associations between characteristics and pre-radiotherapy sleep disorders.*

Characteristic		Sleep disorders, n (%)		
		Yes (n=44)	No (n=59)	*p*-Value
COVID-19 pandemic	Before	25 (57)	27 (46)	0.27
	During	19 (43)	32 (54)	
Age	≤63 Years	28 (64)	26 (44)	**0.049**
	≥64 Years	16 (36)	33 (56)	
Gender	Female	12 (27)	12 (20)	0.41
	Male	32 (73)	47 (80)	
Karnofsky performance score	≤80	27 (61)	18 (31)	**0.002**
	≥90	17 (39)	41 (69)	
Charlson comorbidity index	2	11 (25)	31 (53)	**0.005**
	≥3	33 (75)	28 (47)	
History of another malignancy	No	33 (75)	55 (93)	0.012
	Yes	11 (25)	4 (7)	
Family history of malignancy	No	25 (61)	29 (50)	0.28
	Yes	16 (39)	29 (50)	
Distress-score	0-5	25 (57)	42 (71)	0.13
	6-10	19 (43)	17 (29)	
Number of emotional problems	0-1	14 (32)	38 (64)	**0.001**
	≥2	30 (68)	21 (36)	
Number of physical problems	0-4	10 (23)	45 (76)	**<0.001**
	≥5	34 (77)	14 (24)	
Number of practical problems	0	27 (61)	39 (66)	0.62
	≥1	17 (39)	20 (34)	
Request for psychological support	No	24 (55)	49 (83)	**0.002**
	Yes	20 (45)	10 (17)	
Tumor site	Oropharynx	24 (55)	25 (42)	0.052
	Oral cavity/FoM	6 (14)	16 (27)	
	Hypopharynx	9 (20)	4 (7)	
	Larynx	1 (2)	6 (10)	
	Other	4 (9)	8 (14)	
Primary tumor stage	T1-2	16 (36)	23 (39)	0.79
	T3-4	28 (64)	36 (61)	
Nodal stage	N0	6 (14)	16 (27)	0.099
	N+	38 (86)	43 (73)	
Upfront surgery	No	22 (50)	21 (36)	
	Yes	22 (50)	38 (64)	0.14
Planned concurrent chemotherapy	No	11 (25)	19 (32)	0.43
	Yes	33 (75)	40 (68)	
Brachytherapy boost	No	42 (95)	55 (93)	
	Yes	2 (5)	4 (7)	>0.99

COVID-19: Coronavirus Disease 2019; FoM: floor of mouth; SCC: squamous cell carcinoma. Significant *p*-values are given in bold.

identify patients who are likely to benefit from early psychological support.

In this study, the frequency of sleep disturbances was 42.7%. This frequency was in the range (29-60%) of pre-treatment sleep disorders reported in previous studies (16-19). In 2014, Mo *et al*. presented the data of 51 patients irradiated for cancer of the nasopharynx and reported a prevalence of pre-radiotherapy sleep disturbances of 37.3% (16). In 2021, Wang *et al*. reported a prevalence of 41.7% prior to radiotherapy of nasopharyngeal cancer (17). In 2019, Santoso *et al*. performed a systematic review and meta-analysis on the prevalence of sleep disturbances in patients with head-and-neck cancer but did not focus on radiotherapy (18). The overall frequency of sleep disturbances prior to any treatment was 29%. In another article from Santoso *et al*. in a cross-sectional study of 560 patients with newly diagnosed head-and-neck cancer, poor sleep before the start of treatment was reported by 44% of the patients (19). Moreover, in 2009 and 2011, Savard *et al*. evaluated sleep problems in patients with various primary tumor types (20,

21). Patients with head-and-neck cancer accounted for about 2% in these cohorts. In these subgroups, symptoms of insomnia were found in 30% and 34% of patients, respectively, and symptoms plus criteria for an insomnia syndrome in 60% and 59% of patients, respectively.

Moreover, the current study identified several significant risk factors for pre-radiotherapy sleep disturbances including age ≤63 years, KPS ≤80, CCI ≥3, history of another malignancy, greater numbers of emotional and physical problems, and request for psychological support. These results showed consistency with some findings of two previous studies reporting risk factors for sleep disturbances in patients with head-and-neck cancer (19, 22). In 2007, Duffy *et al*. identified younger age, depressive symptoms (emotional problem), and lower physical activity as risk factors for reduced pre-treatment (at baseline) sleep quality in a cohort of 263 patients with head-and-neck cancer (22). Lower physical activity was likely a result of a lower performance score, a higher comorbidity score and more pronounced physical problems. More recently, in the study of Santoso *et al*., younger age, coping including the expression of emotions and symptoms of cancer belonging to physical problems as assessed by the National Comprehensive Cancer Network Distress Thermometer (5, 6) were significantly associated with poor sleep quality in the univariate analysis (19). Younger age and pain (physical problem) maintained significance in the multivariate analysis.

Moreover, in previous studies evaluating sleep disturbances prior to a course of radiotherapy for breast cancer, the occurrence of sleep problems was significantly associated with younger age, lower performance score, higher comorbidity score, Patient's history of additional breast tumor, number of emotional and physical problems, and patient's request for psychological support (23, 24). However, although the results of the current study are consistent with those from previous studies, given the retrospective nature of our data, the risk of hidden selection biases should be considered when interpreting the results.

In summary, sleep disturbances were frequent in patients assigned to radiotherapy of head-and-neck cancer. Several risk factors were found that can facilitate the identification of patients who may benefit from psychological support offered prior to beginning their radiotherapy course.

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

D.R., S.K., T.B., S.T. and T.W.K designed the study. D.R., S.K. and T.S. provided the data. D.R. and S.E.S. performed the analyses and drafted the article. The article was reviewed and finally approved by all Authors.

Acknowledgements

As part of the project NorDigHealth, this study was funded by the European Regional Development Fund through the Interreg Deutschland-Danmark program.

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Received July 16, 2021
Revised August 9, 2021
Accepted August 23, 2021