

Sleep Problems Prior to Radio-chemotherapy in Patients With Locally Advanced Cancer of the Esophagus or the Esophagogastric Junction

DIRK RADES¹, SVENJA KOPELKE^{1,2}, STEVEN E. SCHILD³,
SOEREN TVILSTED⁴, TROELS W. KJAER⁵ and TOBIAS BARTSCHT^{2,6}

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

²Department of Hematology and Oncology, University of Lübeck, Lübeck, Germany;

³Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.;

⁴Research Department, Zealand University Hospital, Køge, Denmark;

⁵Neurological Department, Zealand University Hospital, Roskilde, Denmark;

⁶Department of Hematology, Oncology and Stem Cell Transplantation, Helios Hospital, Schwerin, Germany

Abstract. *Background/Aim:* Many patients with locally advanced cancer of the esophagus or esophagogastric junction receive definitive or neoadjuvant radio-chemotherapy. Patient anticipation of this treatment can cause or aggravate distress and sleep disorders. This study aimed to identify the prevalence of sleep disorders and risk factors. *Patients and Methods:* Thirty-eight patients assigned to radio-chemotherapy were retrospectively evaluated for pre-treatment sleep disorders. Investigated characteristics included age; sex; performance score; comorbidity index; previous malignancies; family history; distress score; emotional, physical or practical problems; tumor site; histology and grading; tumor stage; planned treatment; and relation to 2019 Coronavirus pandemic. *Results:* Sleep problems were reported by 15 patients (39.5%). Significant associations were found for higher distress scores ($p=0.016$) and greater numbers of emotional problems ($p<0.0001$). A trend was observed for greater numbers of physical problems ($p=0.176$). *Conclusion:* The prevalence of sleep problems

was high. Risk factors were found that can help identify patients requiring psychological support already prior to radio-chemotherapy.

The group of malignant upper gastrointestinal tumors include esophageal cancers, cancers of the esophagogastric junction and gastric cancers. When compared to other solid malignancies, upper gastrointestinal cancers are less common. For example, the annual incidence of esophageal cancer is 8 of 100,000 inhabitants for men and 2 of 100,000 inhabitants for women (1). Many patients with cancer of the esophagus and the esophagogastric junction receive radio-chemotherapy, either alone as definitive treatment or prior to surgery as neoadjuvant treatment. This applies particularly to squamous cell cancers (SCC) that are mainly located in the proximal (upper) two thirds of the esophagus. The majority of the tumors found in more distal locations are adenocarcinomas that are often treated with neoadjuvant chemotherapy followed by surgical resection. The histology of the tumor is associated with sex; the majority (57.4%) of the male patients have adenocarcinomas, whereas the majority (58.6%) of female patients have SCC (2).

Since many patients with esophageal cancer and cancer of the esophagogastric junction present with locally advanced tumors and have unfavorable prognoses, the diagnosis of their malignant disease generally causes significant emotional distress resulting in an impairment of their quality of life. These patients often show symptoms related to this fatal situation including sleep disorders. Moreover, to be scheduled for multimodal anticancer treatment likely leads to an aggravation of the symptoms. It would be helpful to identify patients who likely will suffer from distress and

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: Esophageal cancer, adenocarcinoma of the esophagogastric junction, radio-chemotherapy, sleep problems, prevalence, risk factors.



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Table I. Characteristics evaluated for associations with pre-treatment sleep problems.

Characteristic	Subgroup	Frequency, n (%)
Age	≤70 Years	23 (61)
	≥71 Years	15 (39)
Sex	Female	10 (26)
	Male	28 (74)
Karnofsky performance score	≤80	14 (37)
	≥90	23 (61)
	Unknown	1 (3)
Charlson comorbidity index	≤3	14 (37)
	≥4	24 (63)
History of previous malignancy	No	27 (71)
	Yes	11 (29)
Family history of malignancy	No	24 (63)
	Yes	14 (37)
Distress score	0-3	14 (37)
	≥4	23 (61)
	Unknown	1 (3)
Emotional problems	No	19 (50)
	Yes	19 (50)
Physical problems	No	13 (34)
	Yes	25 (66)
Practical problems	No	29 (76)
	Yes	9 (24)
Tumor site	Esophagus	29 (76)
	AEG	9 (24)
Histology	SCC	25 (66)
	Adenocarcinoma	13 (34)
Histologic grading	G1-2	20 (53)
	G3	15 (39)
	Unknown	3 (8)
Primary tumor stage	T1-2	7 (18)
	T3-4	31 (82)
Nodal stage	N0	5 (13)
	N+	33 (87)
Planned treatment	Neoadjuvant RCT	16 (42)
	Definitive RCT	22 (58)
COVID-19 pandemic	Before	14 (37)
	During	24 (63)

AEG: Adenocarcinoma of the esophagogastric junction; SCC: squamous cell carcinoma; RCT: radio-chemotherapy; COVID-19: Coronavirus Disease 2019.

sleep disorders prior to the start of treatment in order to be able to provide early psychological support.

Currently, very little data are available regarding the prevalence and risk factors of pre-treatment sleep disorders in patients with cancer of the esophagus and the esophagogastric junction. In a study including different types of cancer, 41.5% of the 65 patients with esophageal cancer reported sleep disorders prior to radiotherapy (3). This high rate of sleep problems illustrates the significance of this problem. However, no risk factors were identified for these patients. More studies are required investigating pre-

treatment sleep disorders in patients with cancer of the esophagus or esophagogastric junction. The present study aimed to identify the prevalence of sleep disorders prior to radio-chemotherapy and corresponding risk factors in this group of patients.

Patients and Methods

Thirty-eight patients who were assigned to radio-chemotherapy of locally advanced cancer of the esophagus or esophagogastric junction and completed an evaluation of quality of life prior to their treatment with the National Comprehensive Cancer Network (NCCN) Distress Thermometer (4, 5) were included in this retrospective study, which was approved by the Ethics Committee of University of Lübeck (reference number 21-284). Twenty-nine patients had esophageal cancer, and nine patients had adenocarcinoma of the esophagogastric junction. Radiotherapy was performed as volumetric modulated arc therapy. The treatment volume included the primary tumor and loco-regional lymph nodes. Planned total doses were 41.4-45.0 Gy (5×1.8 Gy per week) for neoadjuvant treatment and 54.0-59.4 Gy (5×1.8 Gy per week) for definitive treatment, respectively. In case of definitive treatment, the initial target volume (up to 45-50.4 Gy) included the primary tumor and loco-regional lymph nodes, which was followed by a boost of 9.0-14.4 Gy to primary tumor and involved lymph nodes. Median administered doses were 41.4 Gy for neoadjuvant and 59.4 Gy for definitive treatment, respectively. The planned concurrent chemotherapy included two courses of cisplatin (20 mg/m²/d1-5) and 5-fluorouracil (1,000 mg/m²/d1-5) or weekly carboplatin (area under the curve 2.0) plus paclitaxel (50 mg/m²). Finally, 18 patients received weekly carboplatin/paclitaxel, nine cisplatin/5-FU, four cisplatin alone, two paclitaxel alone, and five patients could not receive chemotherapy.

Seventeen characteristics (Table I) were evaluated for associations with sleep disorders prior to radio-chemotherapy sleep disorders. These characteristics included age (≤70 vs. ≥71 years, median=70 years); sex (female vs. male); Karnofsky performance score (≤80 vs. ≥90); Charlson comorbidity index (≤3 vs. ≥4); history of previous malignancy (no vs. yes); family history of malignancy (no vs. yes); distress score (0-3 vs. ≥4); numbers of emotional (0-1 vs. ≥2), physical (0-1 vs. ≥2) or practical (no vs. yes) problems according to the NCCN Distress Thermometer (4, 5); tumor site (esophagus vs. AEG); histology (squamous cell carcinoma vs. adenocarcinoma); histologic grading (G1-2 vs. G3); primary tumor stage (T1-2 vs. T3-4); nodal stage (N0 vs. N+); planned treatment (adjuvant vs. definitive radio-chemotherapy); and relation to the 2019 Coronavirus (COVID-19) pandemic (before vs. during). Evaluations of associations between sleep disorders prior to radio-chemotherapy and the 17 characteristics were performed using the Fisher's exact test. *p*-Values <0.05 were considered statistically significant and *p*-values <0.20 indicating a trend.

Results

Sleep disorders occurred in 15 of the 38 patients (39.5%) in the entire cohort, in 10 of 29 patients (34.5%) with esophageal cancer, and in five of nine patients (55.6%) with cancer of the esophagogastric junction, respectively. Significant associations with the occurrence of pre-treatment

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

Characteristic	Subgroup	Sleep disorders, n (%)		p-Value
		Yes (n=15)	No (n=23)	
Age	≤70 Years	11 (73)	12 (52)	0.310
	≥71 Years	4 (27)	11 (48)	
Sex	Female	3 (20)	7 (30)	0.09
	Male	12 (80)	16 (70)	
Karnofsky performance score	≤80	7 (50)	7 (30)	0.30
	≥90	7 (50)	16 (70)	
Charlson comorbidity index	≤6	6 (40)	8 (35)	>0.999
	≥7	9 (60)	15 (65)	
History of previous malignancy	No	11 (73)	16 (70)	>0.999
	Yes	4 (27)	7 (30)	
Family history of malignancy	No	10 (67)	14 (61)	>0.999
	Yes	5 (33)	9 (39)	
Distress-score	0-3	2 (13)	12 (55)	0.016
	≥4	13 (87)	10 (45)	
Emotional problems	No	1 (7)	18 (78)	<0.0001
	Yes	14 (93)	5 (22)	
Physical problems	No	3 (20)	10 (43)	0.176
	Yes	12 (80)	13 (57)	
Practical problems	No	10 (67)	19 (83)	0.437
	Yes	5 (33)	4 (17)	
Tumor site	Esophagus	10 (67)	19 (83)	0.437
	AEG	5 (33)	4 (17)	
Histology	SCC	9 (60)	16 (70)	0.728
	Adenocarcinoma	6 (40)	7 (30)	
Histologic grading	G1-2	8 (53)	12 (60)	0.741
	G3	7 (47)	8 (40)	
Primary tumor stage	T2	1 (7)	6 (26)	0.209
	T3-4	14 (93)	17 (74)	
Nodal stage	N0	1 (7)	4 (17)	0.630
	N+	14 (93)	19 (83)	
Planned treatment	Neoadjuvant RCT	6 (40)	10 (43)	>0.999
	Definitive RCT	9 (60)	13 (57)	
COVID-19 pandemic	Before	6 (40)	8 (35)	>0.999
	During	9 (60)	15 (65)	

AEG: Adenocarcinoma of the esophagogastric junction; SCC: squamous cell carcinoma; RCT: radio-chemotherapy; COVID-19: Coronavirus Disease 2019. Significant *p*-values are given in bold.

sleep problems were found for higher distress scores ($p=0.016$) and greater numbers of emotional problems ($p<0.0001$). Moreover, a trend was observed for greater numbers of physical problems ($p=0.176$). The COVID-19 pandemic was not associated with sleep disorders prior to the radio-chemotherapy course ($p>0.999$) (Table II).

Discussion

Many patients with locally advanced cancer of the esophagus and esophagogastric junction are assigned to radio-chemotherapy. Anticipation of this treatment can lead to or aggravate emotional distress associated with significant sleep disorders. This is mainly due to concerns regarding the

upcoming aggressive treatment, which is associated with severe side effects in the majority of the patients (6-12). Moreover, pre-treatment sleep disorders were reported to be associated with sleep disturbance after esophagectomy (13). Although sleep disorders represent a significant and potentially burdensome problem for the patients, very little data are available regarding the prevalence of sleep disorders prior to a course of radio-chemotherapy for patients with upper gastrointestinal cancers. Only one study reported the prevalence of sleep disorders prior to a course of radiotherapy in patients with esophageal cancer (3). In this study that included 330 eligible patients with different primary tumor types, 27 of 65 patients (41.5%) with esophageal cancer reported sleep disturbances prior to their

course of radiotherapy. This prevalence was similar to the prevalence of 39.5% in the entire cohort of the present study.

Identification of risk factors for the occurrence of sleep disturbances prior to radio-chemotherapy was the second major goal of the present study in addition to determination of its prevalence. Significant associations between sleep disorders were found for higher distress scores and greater numbers of emotional problems, and a trend was found for greater numbers of physical problems. To our knowledge, no study so far has investigated potential risk factors prior to a course of radio-chemotherapy in patients with locally advanced cancer of the esophagus or esophagogastric junction. Therefore, it is difficult to compare the results of the present study to data from the literature. However, these results agree with the results of studies available for pre-treatment sleep problems in patients with lower gastrointestinal cancers, namely with colorectal cancers. In a study of 84 patients with early colorectal cancers, pre-treatment sleep disorders were associated with emotional problems (14). In another previous study, sleep problems at the time of diagnosis of colorectal cancer was significantly associated with the presence of physical problems and also with the presence of emotional problems (15). Moreover, in a cross-sectional study including 434 patients with colorectal cancer, insomnia prior to surgery was significantly associated with pain (physical problem) and anxiety (emotional problem) (16). In a recent study of patients irradiated for rectal or anal cancer, the occurrence of pre-radiotherapy sleep disorders was significantly associated with higher distress scores and greater numbers of emotional and physical problems (17). Moreover, in two previous studies of patients irradiated for malignancies in the thoracic region, namely for breast cancer or lung cancer, higher distress scores and greater numbers of emotional or physical problems were significantly associated with the occurrence of pre-treatment sleep problems (18, 19). However, the comparison of the results of the present study to previous studies performed in patients with other primary tumor types is difficult. In addition, the retrospective nature of the present study bearing the risk of hidden selection biases and its small sample size should be taken into consideration when interpreting the results.

In conclusion, the prevalence of sleep disorders was high, which demonstrates the meaning of this potentially burdensome symptom. The risk factors determined in this study can help identify patients who require psychological support already prior to their planned course of radio-chemotherapy.

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., S.E.S., S.T., T.W.K. and T.B. participated in the design of the study. D.R. and S.K. provided the data that were analyzed by D.R. The article, which was drafted by D.R. and S.E.S., was reviewed and approved by all Authors.

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