

Sleep Disturbances in Lung Cancer Patients Assigned to Definitive or Adjuvant Irradiation

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Abstract. *Background/Aim:* A considerable number of patients with lung cancer are scheduled for definitive or adjuvant radiotherapy. Prevalence and potential risk factors of pre-radiotherapy sleep disturbances were evaluated. *Patients and Methods:* Nineteen factors were retrospectively investigated for associations with pre-radiotherapy sleep disturbances in 77 lung cancer patients. Factors included COVID-19 pandemic; age; gender; performance score; comorbidity index; history of another malignancy; distress score; number of emotional, physical or practical problems; patient's request for psychological support; histology; tumor stage; upfront surgery; chemotherapy; and type of radiotherapy. *Results:* Thirty-one patients (40.3%) reported sleep disturbances that were significantly associated with distress score 6-10 ($p=0.019$), ≥ 2 emotional problems ($p=0.001$), ≥ 5 physical problems ($p<0.001$), and request for psychological support ($p=0.006$). Trends were found for female gender ($p=0.064$) and stereotactic body radiation therapy ($p=0.057$). *Conclusion:* Many lung cancer patients assigned to radiotherapy reported sleep disturbances. Risk factors can be used to identify patients in need of psychological support already before treatment.

Lung cancer is the second most common type of cancer in the Western countries (1). For patients with advanced non-

small cell lung cancer (NSCLC), definitive radiotherapy is indicated for unresectable stage III disease and selected patients with stage IV disease (2). Also, patients who cannot undergo thoracic surgery due to advanced age, poor performance status or high comorbidity index can be treated with definitive radiotherapy. Moreover, after microscopically or macroscopically incomplete resection, patients may receive adjuvant radiotherapy. Radiotherapy is often combined with sequential and/or concurrent cisplatin-based chemotherapy (2). Moreover, patients with tumors ≤ 4 cm without lymph node metastasis who are not candidates for surgery can be treated with stereotactic body radiation therapy (SBRT) using higher doses per fraction than for conventionally fractionated radiotherapy (2, 3).

The majority of patients with small cell lung cancer (SCLC) receive definitive radiotherapy, which is generally combined with sequential and/or concurrent chemotherapy. The standard chemotherapy regimen includes cisplatin and etoposide (2).

Radiotherapy for lung cancer can be associated with serious side effects. Potential acute toxicities include dermatitis, pneumonitis, esophagitis, cardiac arrhythmia, hypothyroidism, loss of appetite, nausea and vomiting, fatigue and pancytopenia (4-6). The possibility of these adverse events and being assigned to a treatment using high-technology and radiation can cause significant emotional distress for the patients associated with sleep disturbances. Studies focusing on sleep disturbances in patients irradiated for lung cancer are rare. The present study aimed to provide additional data for this stressful situation. One major aim was the determination of the prevalence of sleep disturbances prior to a radiation course for lung cancer. In addition, this study aimed to identify risk factors for pre-radiotherapy sleep disturbances. Such risk factors will contribute to the identification of lung cancer patients who likely benefit from psychological support before their radiotherapy course.

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Key Words: Lung cancer patients, sleep disturbances, irradiation, frequency, risk factors.

Patients and Methods

Potential prognostic factors were analyzed for associations with the occurrence of sleep disturbances prior to a planned course of radiotherapy in a cohort of 77 patients with lung cancer. These patients had their first appointment at the department of radiation oncology between March 2019 and February 2021. All patients included in this retrospective study completed the distress thermometer of the National Comprehensive Cancer Network (7, 8). The study was approved by the ethics committee of the University of Lübeck (reference 21-284).

The majority of the patients (n=59) presented with NSCLC, 29 with squamous cell carcinoma, 26 with adenocarcinoma and 4 with NSCLC-NOS (not otherwise specified). In patients with NSCLC, radiotherapy was either definitive (n=50) or adjuvant following thoracic surgery (n=9). In 10 patients with limited stage NSCLC, SBRT alone to the primary tumor region was planned with total doses of 48-64 Gy and doses per fraction of 4-8 Gy. In addition, two patients received SBRT (7×8 Gy and 8×6 Gy, respectively) for radiologically confirmed lung cancer without histological proof.

The other 49 patients with NSCLC were scheduled for conventionally fractionated radiotherapy (volumetric modulated arc therapy=VMAT) to the primary tumor and loco-regional lymph nodes with total doses of 60-70 Gy and doses per fraction of 2 Gy. Twenty-two of these 49 patients were treated with radiotherapy alone. Twenty-four of the other 27 patients had received systemic treatment prior to irradiation including carboplatin/paclitaxel (n=8), cisplatin/vinorelbine (n=7), cisplatin/pemetrexed (n=4), pembrolizumab (n=2), cisplatin/gemcitabine (n=1), carboplatin/vinorelbine (n=1) and trametinib/dabrafenib (n=1). In 13 of these 24 patients, additional systemic treatment was planned during the course of radiotherapy. Additionally, 13 patients were scheduled for concurrent systemic treatment alone with cisplatin/pemetrexed (n=6), cisplatin/vinorelbine (n=5), or paclitaxel weekly (n=2).

Of the 16 patients with SCLC, 15 patients received chemotherapy with cisplatin/etoposide (n=10) or carboplatin/etoposide (n=5), which was administered either prior to radiotherapy only (n=9), before and during radiotherapy (n=5), or during radiotherapy only (n=1). All 16 patients were assigned to conventionally fractionated radiotherapy (volumetric modulated arc therapy) of the primary tumor and loco-regional lymph nodes with planned total doses of 56-66 Gy and doses per fraction of 2 Gy.

A total of 19 potential prognostic factors (Table I) were investigated for associations with sleep disturbances before the start of radiotherapy. Factors included the COVID-19 pandemic (before vs. during); age (≤ 70 vs. ≥ 71 years, median=70 years); gender (female vs. male); Karnofsky performance score (KPS ≤ 80 vs. ≥ 90); Charlson comorbidity index (CCI 2 vs. ≥ 3); history of another 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 distress thermometer (7, 8); patient's request for psychological support (no vs. yes); histology (NSCLC vs. SCLC); primary tumor stage (T1-2 vs. T3-4); nodal stage (N0 vs. N+); metastatic stage (M0 vs. M1); upfront surgery (no vs. yes); upfront chemotherapy (no vs. yes); upfront or planned concurrent chemotherapy (no vs. yes); and type of radiotherapy (conventional fractionation vs. SBRT).

Statistical analyses were performed using the chi-square test or (in case of n<5) the Fisher's exact test. In these analyses, p-values <0.05 were considered demonstrating statistical significance and p-values <0.07 indicating a trend.

Results

In the entire cohort, 31 patients (40.3%) reported sleep disturbances before the planned radiation treatment. Sleep disturbances were significantly associated with a distress score of 6-10 ($p=0.019$), 2 or more emotional problems ($p=0.001$), 5 or more physical problems ($p<0.001$), and patient's request for psychological support ($p=0.006$). In addition, trends for associations with sleep disturbances were found for female gender ($p=0.064$) and planned treatment with SBRT ($p=0.057$). A significant association between sleep disturbances and the COVID-19 pandemic was not observed ($p=0.20$). The results of the entire analyses are summarized in Table II.

Discussion

Many patients with lung cancer receive conventionally fractionated radiotherapy, either as definitive treatment or following incomplete resection (2). In addition, patients with comparably small node-negative NSCLC who are not suitable for surgery can be treated with SBRT (2, 3). Patients scheduled for a high-tech treatment such as modern radiotherapy with VMAT or SBRT may be worried about upcoming radiotherapy and potential treatment-related adverse effects, which may lead to significant distress including sleep disturbances (4-6, 9, 10).

Knowledge of the prevalence of pre-radiotherapy sleep disturbances and corresponding risk factors in patients assigned to radiotherapy for lung cancer will allow identification of patients requiring early psychological intervention and provision of early support. The present study aimed to determine both prevalence and risk factors of sleep disturbances prior to radiation treatment. The prevalence of pre-radiotherapy sleep disturbances was 40.3%, which was similar to the prevalence of 45.2% in the only previous study that reported a prevalence of pre-radiotherapy sleep disturbances in patients irradiated for lung cancer (11). In addition, the prevalence of sleep disturbances in lung cancer patients have been reported in different pre-treatment situations than before radiotherapy. For example, Belloumi *et al.* reported a prevalence of 15% prior to chemotherapy (12), and Halle *et al.* a prevalence of 60.9% prior to surgery (13). Moreover, Nishiura *et al.* found a prevalence of 56% in lung cancer patients who were admitted to hospital or already in-patients, regardless of the type of treatment (14). In addition, Bülbül *et al.* reported rates of 48.4% for difficulty initiating or maintaining sleep (DIMS) and of 44.7% for insomnia in a large unspecified cohort of 1,245 patients with lung cancer (15).

In addition to the prevalence of sleep disturbances, we identified several significant risk factors for their occurrence including a higher distress score, greater numbers of emotional and physical problems, and patient's request for psychological

Table I. Potential risk factors evaluated for sleep disturbances.

Factor	Frequency, n (%)
Coronavirus disease 2019 (COVID-19) pandemic	
Before	44 (57)
During	33 (43)
Age	
≤70 Years	40 (52)
≥71 Years	37 (48)
Gender	
Female	21 (27)
Male	56 (73)
Karnofsky performance score	
≤80	25 (32)
≥90	52 (68)
Charlson comorbidity index	
2	38 (49)
≥3	39 (51)
History of another malignancy	
No	52 (68)
Yes	25 (32)
Distress-score	
0-5	47 (61)
6-10	30 (39)
Number of emotional problems	
0-1	46 (60)
≥2	31 (40)
Number of physical problems	
0-4	44 (57)
≥5	33 (43)
Number of practical problems	
0	56 (73)
≥1	21 (27)
Request for psychological support	
No	69 (90)
Yes	8 (10)
Histology	
NSCLC	59 (77)
SCLC	16 (21)
Unknown	2 (3)
Primary tumor stage	
T1-2	28 (36)
T3-4	48 (62)
Unknown	1 (1)
Nodal stage	
N0	26 (34)
N+	48 (62)
Unknown	3 (4)
Metastatic stage	
M0	60 (78)
M1	15 (19)
Unknown	2 (3)
Upfront surgery	
No	68 (88)
Yes	9 (12)
Upfront chemotherapy	
No	39 (51)
Yes	38 (49)
Upfront or planned concurrent chemotherapy	
No	25 (32)
Yes	52 (68)
Type of radiotherapy	
EBRT	65 (84)
SBRT	12 (16)

NSCLC: Non-small cell lung cancer; SCLC: small-cell lung cancer; EBRT: external beam radiation therapy; SBRT: stereotactic body radiation therapy.

Table II. Associations between potential risk factors and sleep disturbances prior to a planned course of radiotherapy.

Factor	Sleep disturbances, n (%)		
	Yes (n=31)	No (n=46)	p-Value
Coronavirus disease 2019 (COVID-19) pandemic			
Before	15 (48)	29 (63)	0.20
During	16 (52)	17 (37)	
Age			
≤70 Years	14 (45)	26 (57)	0.33
≥71 Years	17 (55)	20 (43)	
Gender			
Female	12 (39)	9 (20)	0.064
Male	19 (61)	37 (80)	
Karnofsky performance score			
≤80	11 (35)	14 (30)	0.64
≥90	20 (65)	32 (70)	
Charlson comorbidity index			
2	12 (39)	26 (57)	0.13
≥3	19 (61)	20 (43)	
History of another malignancy			
No	19 (61)	33 (72)	0.34
Yes	12 (39)	13 (28)	
Distress-score			
0-5	14 (45)	33 (72)	0.019
6-10	17 (55)	13 (28)	
Number of emotional problems			
0-1	10 (32)	36 (78)	<0.001
≥2	21 (68)	10 (22)	
Number of physical problems			
0-4	10 (32)	34 (74)	<0.001
≥5	21 (68)	12 (26)	
Number of practical problems			
0	20 (65)	36 (78)	0.18
≥1	11 (35)	10 (22)	
Request for psychological support			
No	24 (77)	45 (98)	0.006
Yes	7 (23)	1 (2)	
Histology			
NSCLC	21 (70)	38 (84)	0.13
SCLC	9 (30)	7 (16)	
Primary tumor stage			
T1-2	12 (39)	16 (36)	0.78
T3-4	19 (61)	29 (64)	
Nodal stage			
N0	13 (42)	13 (30)	0.30
N+	18 (58)	30 (70)	
Metastatic stage			
M0	26 (84)	34 (77)	0.48
M1	5 (16)	10 (23)	
Upfront surgery			
No	29 (94)	39 (85)	0.30
Yes	2 (6)	7 (15)	
Upfront chemotherapy			
No	15 (48)	24 (52)	0.74
Yes	16 (52)	22 (48)	
Upfront or planned concurrent chemotherapy			
No	10 (32)	15 (33)	0.97
Yes	21 (68)	31 (67)	
Type of radiotherapy			
EBRT	23 (74)	42 (91)	0.057
SBRT	8 (26)	4 (9)	

NSCLC: Non-small cell lung cancer; SCLC: small-cell lung cancer; EBRT: external beam radiation therapy; SBRT: stereotactic body radiation therapy. Significant p-values are shown in bold.

support. Moreover, trends for a positive correlation with the occurrence of pre-radiotherapy sleep disturbances were found for female gender and planned SBRT.

These results showed consistency with findings of previous studies that reported risk factors for sleep disturbances in patients with lung cancer (12-17). In the study of Belloumi *et al.* that included 64 patients with stage III or IV NSCLC, sleep disturbances prior to chemotherapy were associated with emotional problems, namely with depression and anxiety (12). The study of Halle *et al.* investigated sleep disturbances in patients undergoing surgery for lung cancer (13). Sleep disturbances were associated with several factors including the use of psychotropic medication (indicator of psychological problems) and use of pain medication. In the distress thermometer of the National Comprehensive Cancer Network, pain is rated as a physical problem (7, 8). In contrast to our study, younger age and higher comorbidity score were also associated with sleep disturbances (13). Nishiura *et al.* found significant associations of sleep disturbances with pain, depression and anxiety (14), and Bülbül *et al.* associations with female gender, anxiety and symptoms of lung cancer (15). The distress thermometer of the National Comprehensive Cancer Network rates symptoms such as dyspnea, pain, fatigue, and fever as physical problems (7, 8). The trend for an increased rate of sleep disturbances in patients scheduled for SBRT was not reported before. To our knowledge, this aspect has not yet been investigated. Thus, one can only hypothesize. SBRT with higher doses per fraction may be felt by the patients as being more aggressive than conventional radiotherapy, particularly if it is explained to the patients as a type of radio-surgery. Interestingly, the prevalence of sleep disturbances in patients assigned to surgery for lung cancer was 60.9% and, therefore, considerably higher than prior to radiotherapy in the present study (40.3%) and a previous study (45.2%) (11, 13).

In addition to these studies of lung cancer patients, in two previous studies that investigated pre-radiotherapy sleep disturbances in patients with breast cancer and used the same approach as the present study, distress score, numbers of emotional and physical problems, and request for psychological support were also significantly associated with sleep disturbances (16, 17). When interpreting the results of the present study, one should bear in mind its retrospective design, which bears the risk of a hidden bias, although it appears consistent with the results of previous studies.

In summary, many lung cancer patients assigned to radiotherapy reported sleep disturbances. Several risk factors were determined that will help identify patients who need psychological support already before 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

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

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