

Evaluation of Pre-radiotherapy Sleep Disorders in Patients With Rectal or Anal Cancer

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Abstract. *Background/Aim: Radiotherapy and radiochemotherapy are common treatments for rectal and anal cancer. Anticipation of treatment may cause distress and sleep disorders. This study aimed to identify risk factors for sleep disorders. Patients and Methods: In 42 patients with rectal or anal cancer scheduled for radiotherapy, 16 characteristics were analyzed for associations with pre-radiotherapy sleep disorders including age, gender, performance score, comorbidity, patient's or family history of additional cancer/melanoma, distress score, emotional/physical/practical problems, tumor site and stage, surgery and relation to COVID-19 pandemic. Results: Overall prevalence of pre-radiotherapy sleep disorders was 42.9%. Sleep disorders were significantly associated with Karnofsky performance score 60-80 ($p=0.044$), Charlson comorbidity index ≥ 3 ($p=0.0012$), distress score 6-10 ($p=0.00012$), and more emotional ($p=0.0012$), physical ($p=0.0004$) or practical ($p=0.033$) problems. A trend was found for female gender ($p=0.061$). Conclusion: Sleep disorders were common in patients with rectal or anal cancer scheduled for radiotherapy. Risk factors can help identify patients requiring psycho-oncological support already prior to the start of radiotherapy.*

Colorectal cancer is one of the most common cancer types worldwide (1). Standard treatment for rectal cancer (at least of the lower and middle third) includes radiotherapy or radiochemotherapy of the primary tumor region and the loco-regional lymph nodes (2, 3). This applies also to the

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treatment of cancer of the anal canal (4, 5). The upcoming treatment may cause distress often associated with sleep disorders. In a study of patients receiving local or loco-regional radiotherapy for breast or prostate cancer, the patients reported the most pronounced sleep disturbances prior to the start or during the first week of their radiation treatment (6). However, data regarding pre-treatment sleep disorders of patients scheduled for local or loco-regional radiotherapy of rectal or anal cancer are very scarce. Therefore, we initiated this study to determine the prevalence of pre-radiotherapy sleep problems in these patients and to identify corresponding risk factors. The knowledge of such risk factors will help identify patients who may benefit from psycho-oncological support starting as soon as possible.

Patients and Methods

Data of 42 patients who were scheduled for radiotherapy for rectal or anal cancer and completed the National Comprehensive Cancer Network Distress Thermometer evaluation were retrospectively analyzed for sleep disorders (7, 8). The study was approved by the responsible ethics committee (University of Lübeck, number 21-284).

Thirty patients had rectal cancer and 12 patients had anal cancer, respectively. Radiotherapy was performed as volumetric modulated arc therapy. The median total dose was 50.4 Gy (range=25–61.2 Gy), and the median dose per fraction was 1.8 Gy (range=1.8–5.0 Gy). The treatment volume was planned to include the region of the primary tumor and the loco-regional lymph nodes. Planned concurrent chemotherapy was 5-fluorouracil (5-FU) or capecitabine for rectal cancer and mitomycin plus 5-FU for anal cancer. One patient not suitable for 5-FU/capecitabine received cetuximab plus encorafenib, and one patient with small-cell rectal cancer carboplatin plus etoposide. Concurrent chemotherapy was not given in four patients. Two patients with rectal cancer opted for short-course radiotherapy with 5×5 Gy instead of long-course radiochemotherapy. Two patients with anal cancer experienced deterioration of their performance status between the first contact and start of radiotherapy; one of these patients received palliative radiotherapy with 11×3 Gy, and the other patient could not receive radiotherapy at all.

Sixteen patient and tumor characteristics (Table I) were analyzed for potential associations with pre-radiotherapy sleep disorders including age (≤ 67 vs. ≥ 68 years, median=67 years); gender (female vs. male); Karnofsky performance score (60-80 vs. 90-100); Charlson comorbidity index (2 vs. ≥ 3 , median=3); patient's or family history of additional cancer or melanoma (no vs. yes); distress score (0-5 vs. 6-10; median=5); number of emotional (0-1 vs. ≥ 2 , median=2), physical (0-3 vs. ≥ 4 , median=3) or practical (0 vs. ≥ 1 , median=0) problems according to the National Comprehensive Cancer Network Distress Thermometer (7, 8); primary tumor site (rectum vs. anal canal); primary tumor stage (T2-3 vs. T4); nodal stage (N0 vs. N+); distant metastasis (M0 vs. M1); upfront surgery (no vs. yes); and relation to COVID-19 pandemic (before vs. during).

Statistical analyses for evaluations of potential associations between pre-radiotherapy sleep disorders and the 16 characteristics were performed with the chi-square test or (for $n < 5$) the Fisher's exact test. p -Values < 0.05 were regarded statistically significant, and p -values < 0.07 indicated a trend.

Results

The prevalences of sleep disorders prior to radiotherapy were 42.9% (18 of 42 patients) in the entire cohort, 40.0% (12 of 30 patients) in patients with rectal cancer and 50.0% (6 of 12 patients) in patients with anal cancer. The occurrence of pre-radiotherapy sleep disorders was significantly associated with Karnofsky performance score of 60-80 ($p=0.044$), a Charlson comorbidity index of ≥ 3 ($p=0.0012$), a distress score of 6-10 ($p=0.00012$), ≥ 2 emotional problems ($p=0.0012$), ≥ 4 physical problems ($p=0.0004$), and ≥ 1 practical problem ($p=0.033$) (Table II). In addition, a trend was found for female gender ($p=0.061$). The COVID-19 pandemic was not associated with sleep disorders ($p=0.65$).

Discussion

Anticipation of a course of radiotherapy can lead to distress due to fears and about the unknown technology, exposure to radiation, and potential radiation-associated adverse events (2-5, 9, 10). Pre-treatment distress may cause sleep problems. Data regarding the prevalence of pre-treatment sleep disorders in patients with rectal or anal cancer are extremely scarce. One study reported a prevalence of 30.0% in patients with colorectal cancer prior to radiotherapy, and in another study, the prevalence of insomnia was 38.2% prior to surgery for colorectal cancer (11, 12). For patients with anal cancer, we found no information regarding the prevalence of pre-treatment sleep disorders. In the present study, the prevalence of pre-radiotherapy sleep disorders was 40.0% in patients with rectal cancer. This frequency is similar to those previously reported for patients with colorectal cancer. In our study, the prevalence in patients with anal cancer was a bit higher (50.0%).

In addition to the determination of the prevalence of sleep disorders, we aimed to identify risk factors to help detect those patients who would likely benefit from early psycho-

oncological support. Occurrence of sleep disorders was significantly associated with poorer performance status, higher comorbidity index, higher distress score, and greater numbers of emotional, physical or practical problems. Moreover, female patients were more likely to experience pre-radiotherapy sleep problems. These results agree with the few data available for pre-treatment sleep disorders in patients with colorectal cancer.

In 2016, Hyphantis *et al.* investigated sleep difficulties in 84 patients with early non-metastatic colorectal cancer at different time points over a period of one year (13). Prior to the start of anticancer treatment, sleep problems were associated with emotional problems, namely depression and anxiety, and with female gender. In 2018, Coles *et al.* evaluated the sleep quality in 613 patients diagnosed with colorectal cancer (14). The occurrence of sleep disturbance after diagnosis (prior to the start of treatment) was significantly associated with physical problems such as pain, emotional problems such as anxiety, and with greater comorbidity. Similar results were reported by Sun *et al.* who presented a cross-sectional study of 434 Chinese patients with colorectal cancer in 2020 (12). Pre-surgery sleep disorders were significantly associated with pain and anxiety. In addition, a significant association between pre-treatment sleep disorders and a greater number of comorbidities was found in a study of patients with colorectal cancer, lung cancer or lymphoma prior to the initiation of chemotherapy (15). Moreover, significant associations between pre-radiotherapy sleep disorders and risk factors identified in the present study including a lower Karnofsky performance score, a higher Charlson comorbidity index, a higher distress score, and greater numbers of emotional, physical and practical problems were previously reported for patients with breast cancer (16, 17). However, although the results of the present study agree with the findings of previous studies, the retrospective nature and the small sample size need to be considered during the interpretation of these results.

In summary, pre-radiotherapy sleep disorders were common in patients with rectal or anal cancer. Several significant risk factors for the occurrence of such sleep problems were detected that can help identify patients who require early psycho-oncological support already prior to the start of radiotherapy.

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

Table I. Characteristics analyzed for associations with pre-radiotherapy sleep disorders.

Characteristic	Frequency, n (%)
Age	
≤67 Years	22 (52)
≥68 Years	20 (48)
Gender	
Female	21 (50)
Male	21 (50)
Karnofsky performance score	
60-80	16 (38)
90-100	26 (62)
Charlson comorbidity index	
2	17 (40)
≥3	25 (60)
History of another malignancy	
No	31 (74)
Yes	11 (26)
Family history of malignancy	
No	17 (40)
Yes	25 (60)
Distress score	
0-5	23 (55)
6-10	18 (43)
Unknown	1 (2)
Number of emotional problems	
0-1	17 (40)
≥2	25 (60)
Number of physical problems	
0-3	23 (55)
≥4	19 (45)
Number of practical problems	
0	31 (74)
≥1	11 (26)
Tumor site	
Rectum	30 (71)
Anal canal	12 (29)
Primary tumor stage	
T2-3	35 (83)
T4	7 (17)
Nodal stage	
N0	21 (50)
N+	21 (50)
Distant metastasis	
M0	35 (83)
M1	7 (17)
Upfront surgery	
No	34 (81)
Yes	8 (19)
COVID-19 pandemic	
Before	17 (40)
During	25 (60)

RT: Radiotherapy; COVID-19: Coronavirus Disease 2019.

Table II. Correlations between characteristics and pre-radiotherapy sleep disorders.

Characteristic	Sleep disorders, n (%)		
	Yes (n=18)	No (n=24)	p-Value
Age			
≤67 Years	10 (56)	12 (50)	0.72
≥68 Years	8 (44)	12 (50)	
Gender			
Female	12 (67)	9 (38)	0.061
Male	6 (33)	15 (63)	
Karnofsky performance score			
60-80	10 (56)	6 (25)	0.044
90-100	8 (44)	18 (75)	
Charlson comorbidity index			
2	2 (11)	15 (63)	0.0012
≥3	16 (89)	9 (38)	
History of another malignancy			
No	14 (78)	17 (71)	0.73
Yes	4 (22)	7 (29)	
Family history of malignancy			
No	8 (44)	9 (38)	0.65
Yes	10 (56)	15 (63)	
Distress-score			
0-5	4 (22)	19 (83)	0.0002
6-10	14 (78)	4 (17)	
Number of emotional problems			
0-1	2 (11)	15 (63)	0.0012
≥2	16 (89)	9 (38)	
Number of physical problems			
0-3	4 (22)	19 (79)	0.0004
≥4	14 (78)	5 (21)	
Number of practical problems			
0	10 (56)	21 (88)	0.033
≥1	8 (44)	3 (13)	
Tumor site			
Rectum	12 (67)	18 (75)	0.55
Anal canal	6 (33)	6 (25)	
Primary tumor stage			
T2-3	14 (78)	21 (88)	0.44
T4	4 (22)	3 (13)	
Nodal stage			
N0	10 (56)	11 (46)	0.53
N+	8 (44)	13 (54)	
Distant metastasis			
M0	14 (78)	21 (88)	0.44
M1	4 (22)	3 (13)	
Upfront surgery			
No	13 (72)	21 (88)	0.26
Yes	5 (28)	3 (13)	
COVID-19 pandemic			
Before	8 (44)	9 (38)	0.65
During	10 (56)	15 (63)	

RT: Radiotherapy; COVID-19: Coronavirus Disease 2019; Significant p-values in bold.

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