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Sleep Disorders Prior to Adjuvant Radiation Therapy for Gynecological Malignancies

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Abstract. *Background/Aim: Many patients with gynecological malignancies receive postoperative radiotherapy, which can lead to fear and sleep disorders. We aimed to identify the prevalence of and risk factors for sleep disorders. Patients and Methods: Sixty-two patients assigned to radiotherapy for gynecological malignancies were retrospectively evaluated. Seventeen characteristics were analyzed for associations with pre-radiotherapy sleep disorders including age, Karnofsky performance score, Charlson comorbidity index, history of additional malignancy, family history of gynecological cancer, distress score, emotional, physical or practical problems, tumor site/stage; chemotherapy, treatment volume, brachytherapy, and the COVID-19 pandemic. Results: The prevalence of pre-radiotherapy sleep disorders was 46.8%. Sleep disorders were significantly associated with Charlson comorbidity index ≥3 (p=0.012), greater number of physical problems (p<0.0001), and advanced primary tumor stage (p=0.005). A trend was found for greater number of emotional problems (p=0.075). Conclusion: Pre-radiotherapy sleep disorders are common in patients with gynecological malignancies, particularly in those with specific risk factors. Patients should be offered early psychological support.*

After breast cancer, gynecological malignancies represent the second most common group of female cancers (1). Many of these patients receive local or locoregional radiotherapy, either with external beam radiotherapy (EBRT), brachytherapy or both. Anticipation of a course of radiotherapy can lead to fear and nervousness about the high-tech machinery, exposure to radiation, and potential treatment-related adverse events (2, 3). One potential consequence of these concerns is the occurrence of sleep disorders.

In the studies of Savard *et al*., patients with gynecological malignancies had a high prevalence of insomnia compared to many other primary tumor types (4, 5). Moreover, in a study of patients irradiated for breast or prostate cancer, sleep disorders occurred mainly before or during the initial phase of treatment (6). Very limited data are available regarding the prevalence of pre-treatment sleep disorders and corresponding risk factors in patients receiving postoperative radiotherapy for gynecological cancers. Therefore, the present study aimed to identify risk factors for occurrence of pre-radiotherapy sleep disorders in these patients. These risk factors can contribute to the identification of patients who need early psychological support.

Patients and Methods

Sixty-two patients assigned to postoperative radiation therapy for a gynecological malignancy who completed the evaluation of distress using the National Comprehensive Cancer Network Distress Thermometer (7, 8) were included in this retrospective study, which received approval from the ethics committee of the University of Lübeck (reference number: 21-284). Thirty-three patients had uterine cancer (endometrial carcinoma), 26 cervix cancer, two vulvar cancer, and one patient vaginal cancer. Thirty-five patients received EBRT alone to the region of the primary tumor and the loco-regional lymph nodes with total doses ranging between 45.0 Gy and 64.8 Gy (median dose=50.4 Gy) and a dose per fraction of 1.8 Gy. Four patients were treated with 50.4 Gy of EBRT plus brachytherapy (3×7 Gy, one fraction per week) as a boost. Twenty-three patients received brachytherapy (4×5 Gy, one fraction per week) alone, mainly for T1-tumors. Five patients had received

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chemotherapy only prior to the start of radiotherapy, four of these patients with carboplatin/paclitaxel for endometrial carcinoma and one patient with cisplatin/etoposide for small cell carcinoma of the uterine cervix. One patient received carboplatin/paclitaxel both before and during the course of radiotherapy. In additional 24 patients, concurrent chemotherapy was administered only during the radiotherapy course. Twenty-three patients received weekly cisplatin or carboplatin for cancer of the cervix (n=22) or the vagina (n=1), and one patient two cycles of mitomycin C (days 1 and 29 of the radiotherapy course). In two additional patients, weekly cisplatin was planned but not given due to patient's refusal or co-morbidity.

Sleep disorders (no *vs.* yes) were assessed prior to radiotherapy. A total of 17 patient and tumor characteristics were evaluated for associations with the occurrence of sleep disorders. These characteristics included age (≤63 *vs.* ≥64 years, median=63.5 years); Karnofsky performance score (60-80 *vs.* 90-100); Charlson comorbidity index (2 *vs.* ≥3, median=2); history of previous or concurrent malignancy (no *vs.* yes); family history of gynecological cancer (no *vs.* yes); distress score (0-5 *vs.* 6-10; median=5) according to the National Comprehensive Cancer Network Distress Thermometer (7, 8); number of emotional (0-1 *vs.* ≥2, median=1.5), physical (0-3 *vs.* ≥4, median=4) or practical (0 *vs.* ≥1, median=0) problems according to the Distress Thermometer; tumor site (cervix *vs.* uterus *vs.* vagina/vulva); primary tumor stage (T1-2 *vs.* T3-4); nodal stage (N0 *vs.* N+); distant metastasis (no=M0 *vs.* yes=M1); chemotherapy prior to or during the radiotherapy course (no *vs.* yes); treatment volume of radiotherapy (without *vs.* with loco-regional lymph nodes); brachytherapy (no *vs.* yes); and time-related reference to the COVID-19 pandemic (before *vs.* during the pandemic). The distributions of these characteristics are summarized in Table I.

For the statistical analyses regarding associations between the 17 characteristics and pre-radiotherapy sleep disorders, the chi-square test and the Fisher's exact test (in case of n<5) were used. *p*-Values <0.05 were considered to indicate significance and *p*-values <0.08 to indicate a trend for an association with sleep disorders.

Results

The prevalence of pre-radiotherapy sleep disorders in the entire cohort was 46.8% (29 of 62 patients). Sleep disorders were significantly associated with a Charlson comorbidity index of ≥3 ($p=0.012$), greater number of physical problems ($p<0.0001$), and more advanced primary tumor stage (T3-4, $p=0.005$). Moreover, a trend was observed for a greater number of emotional problems ($p=0.075$) (Table II). The COVID-19 pandemic had no significant impact on the occurrence of pre-radiotherapy sleep disorders ($p=0.33$).

Discussion

Many patients with gynecological cancer receive radiotherapy and/or chemotherapy, which can cause sleep disorders due to fear and nervousness (9-11). The prevalence of sleep disorders in patients with gynecological malignances reported in the literature ranged between 25% and 68% (4, 5, 12-14). In two previous studies, prevalence of insomnia in patients with gynecological malignancies ranged from 33 to 68% and from 49 to 68%, respectively, and was higher than in most patients with other primary tumors (4, 5). Moreover, in a study of 330 cancer patients, the prevalence of sleep disturbances was 43.8% in patients with cervix cancer, which was the second highest cancer-specific prevalence following lung cancer (prevalence=45.2%) (14). However, no study has been reported that focused particularly on sleep disorders prior to a course of postoperative radiotherapy for gynecological cancer and the corresponding risk factors.

This study was performed to fill this gap, since the determination of such risk factors would help identify patients requiring early psychological support. The occurrence of pre-radiotherapy sleep disorders was significantly associated with Charlson comorbidity index, number of physical problems, and primary tumor stage. In addition, the number of emotional problems showed a trend. These findings agree with the results of previous studies that investigated sleep problems in patients wirh gynecological cancers but did not focus on pre-radiotherapy sleep disorders. Aquil *et al.* performed a cross-sectional study of 100 patients with gynecological cancer who underwent radical surgery and found significant correlations between sleep disorders and emotional problems such as anxiety and depression (15). In the study of Sandadi *et al.*, 86 patients with ovarian, fallopian tube or primary peritoneal cancer during the last 5 years completed a questionnaire (16). Thirty-one patients (36%) had current disease, of whom 81% received chemotherapy. Sleep disorders were significantly associated with physical ($p<0.001$), functional ($p<0.001$), and emotional ($p<0.001$) problems. Similar to our study, no significant associations were found between sleep disorders and age or previous chemotherapy. Associations between sleep disorders and physical and emotional problems were also found in two previous studies investigating pre-radiotherapy sleep disorders in breast cancer patients (17, 18). Moreover, in one of these studies, a trend was observed for an association between sleep disorders and a higher Charlson comorbidity index (17). According to our knowledge, associations between a more advanced primary tumor stage and pre-treatment sleep disorders were not previously reported for patients irradiated for gynecological malignancies. However, the fact that more advanced tumors are associated with worse prognoses likely had an effect on emotional problems and distress and, subsequently, on the occurrence of sleep disorders. Despite some consistency with the results of previous reports, the limitations of the present study, in particular its retrospective design and the comparably small patient number should be kept in mind.

In conclusion, pre-radiotherapy sleep disorders are common in patients with gynecological malignancies, particularly in case of risk factors such as Charlson comorbidity index ≥3, advanced primary tumor stage, or higher numbers of physical and emotional problems. Particularly patients with one or more of these risk factors should be offered early psychological support.

Table I. *Characteristics investigated for sleep disorders prior to radiotherapy.*

Characteristic	Frequency, n (%)
Age	
≤63 Years	31 (50)
≥64 Years	31 (50)
Karnofsky performance score	
60-80	20 (32)
90-100	42 (68)
Charlson comorbidity index	
2	34 (55)
≥3	28 (45)
History of another malignancy	
No	50 (81)
Yes	12 (19)
Family history of gynecological cancer	
No	51 (82)
Yes	7 (11)
Unknown	4 (6)
Distress score	
0-5	40 (65)
6-10	22 (35)
Number of emotional problems	
0-1	31 (50)
≥2	31 (50)
Number of physical problems	
0-3	27 (44)
≥4	35 (56)
Number of practical problems	
0	44 (71)
≥1	18 (29)
Tumor site	
Cervix	26 (42)
Uterus	33 (53)
Vagina/Vulva	3 (5)
Primary tumor stage	
T1-2	45 (73)
T3-4	17 (27)
Nodal stage	
N0	41 (66)
N+	21 (34)
Distant metastasis	
M0	55 (89)
M1	7 (11)
Chemotherapy prior to or during RT	
No	31 (50)
Yes	31 (50)
Treatment volume of RT	
Without LN	23 (37)
With LN	39 (63)
Brachytherapy	
No	17 (27)
Yes	45 (73)
COVID-19 pandemic	
Before	34 (55)
During	28 (45)

LN: Lymph nodes; RT: radiotherapy; COVID-19: Coronavirus Disease 2019.

Table II. *Associations of characteristics with sleep disorders prior to radiotherapy.*

	Sleep disorders, n (%)		
Characteristic	Yes (n=29)	No (n=33)	*p*-Value
Age			
≤63 Years	16 (55)	15 (45)	0.45
≥64 Years	13 (45)	18 (55)	
Karnofsky performance score			
60-80	12 (41)	8 (24)	0.15
90-100	17 (59)	25 (76)	
Charlson comorbidity index			
2	11 (38)	23 (70)	**0.012**
≥3	18 (62)	10 (30)	
History of another malignancy			
No	22 (76)	28 (85)	0.37
Yes	7 (24)	5 (15)	
Family history of gynecological cancer			
No	22 (81)	29 (94)	0.23
Yes	5 (19)	2 (6)	
Distress-score			
0-5	17 (59)	23 (70)	0.36
6-10	12 (41)	10 (30)	
Number of emotional problems			
0-1	11 (38)	20 (61)	0.075
≥2	18 (62)	13 (39)	
Number of physical problems			
0-3	4 (14)	23 (70)	**<0.0001**
≥4	25 (86)	10 (30)	
Number of practical problems			
0	18 (62)	26 (79)	0.15
≥1	11 (38)	7 (21)	
Tumor site			
Cervix	13 (45)	13 (39)	0.84
Uterus	15 (52)	18 (55)	
Vagina/Vulva	1 (3)	2 (6)	
Primary tumor stage			
T1-2	16 (55)	29 (88)	**0.005**
T3-4	13 (45)	4 (12)	
Nodal stage			
N0	20 (69)	21 (64)	0.66
N+	9 (31)	12 (36)	
Distant metastasis			
M0	24 (83)	31 (94)	0.24
M1	5 (17)	2 (6)	
Chemotherapy prior to or during RT			
No	13 (45)	18 (55)	0.45
Yes	16 (55)	15 (45)	
Treatment volume of RT			
Without LN	12 (41)	11 (33)	0.51
With LN	17 (59)	22 (67)	
Brachytherapy			
No	9 (31)	8 (24)	0.55
Yes	20 (69)	25 (76)	
COVID-19 pandemic			
Before	14 (48)	20 (61)	0.33
During	15 (52)	13 (39)	

LN: Lymph nodes; RT: radiotherapy; COVID-19: Coronavirus Disease 2019. Statistically significant *p*-values are shown in bold.

Conflicts of Interest

The Authors have no conflicts of interest related to this study.

Authors' Contributions

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

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