

# Sleep Disorders in Patients With Breast Cancer Prior to a Course of Radiotherapy – Prevalence and Risk Factors

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**Abstract.** *Background/Aim:* Most patients with breast cancer are assigned to radiotherapy, which may cause fears leading to sleep disorders. Very few data are available regarding the prevalence of sleep disorders and corresponding risk factors. *Patients and Methods:* Data of 175 patients with breast cancer presenting for adjuvant radiotherapy were retrospectively analyzed. Twenty-three patient and tumor characteristics were investigated for associations with pre-radiotherapy sleep disorders. *Results:* Seventy-eight patients (44.6%) stated sleep disorders prior to radiotherapy. These were significantly associated with higher distress score ( $p<0.0001$ ); greater number of emotional ( $p<0.0001$ ), physical ( $p<0.0001$ ) or practical problems ( $p<0.001$ ); and request for psycho-oncological support ( $p<0.001$ ). Trends were found for worse performance status ( $p=0.062$ ) and higher comorbidity index ( $p=0.059$ ). *Conclusion:* Sleep disorders prior to radiotherapy for breast cancer are common. This applies particularly to patients with risk factors including distress due to emotional, physical or practical problems. These patients should be offered psycho-oncological support as soon as possible.

Breast cancer is one of the most common types of solid cancer in Western countries (1). Most patients with non-metastatic breast cancer receive adjuvant local or locoregional radiotherapy, either following breast-conserving surgery or mastectomy (2). The fact that a patient needs to be irradiated may cause then fear about the unknown technology, exposure to radiation and potential side-effects of the treatment. These

fears and other factors can lead to sleep disorders. According to a previous study, sleep disorders are more common in patients with breast cancer than in those with prostate cancer (3). In another study, most sleep disorders were reported by patients to occur prior to and at the beginning of the course of radiotherapy (4). However, sleep disorders may also increase during the period of treatment as a result of acute toxicity (5). Only very few data exist regarding the prevalence of sleep disorders prior to a radiotherapy course and of potential risk factors (6, 7). Thus, additional studies are needed to identify and support patients suffering from stressful sleep problems. The present study was performed to determine the prevalence of sleep disorders prior to radiotherapy and to identify significant risk factors in a cohort of patients with breast cancer assigned to adjuvant radiotherapy.

## Patients and Methods

A total of 175 patients with breast cancer who presented for adjuvant external beam radiotherapy and completed a National Comprehensive Cancer Network Distress Thermometer evaluation (8, 9) between March 2020 and February 2021 were included in this retrospective study. Patients assigned to brachytherapy or to external beam radiotherapy for a local or locoregional recurrence were not included. The study was approved by the ethics committee of the University of Lübeck (reference 21-128). After breast-conserving surgery, the patients received whole breast irradiation, either with  $15 \times 2.667$  Gy over 3 weeks or  $28 \times 1.8$  Gy over 6.5 weeks (2). Patients younger than 51 years and those 51 years or older with risk factors for local recurrence received a boost to the tumor bed of  $5 \times 2.0$  Gy over 1 week. After mastectomy, radiotherapy of the chest wall was performed in the case of pT4 tumor, pT3 tumor plus risk factors, incomplete resection, involvement of more than three axillary lymph nodes, and involvement of one to three axillary lymph nodes plus risk factors (2). Following neoadjuvant systemic treatment and breast-conserving surgery, radiotherapy was performed in cases of cT3/cT4 tumor, ypT1 or ypN+, and after complete response to systemic treatment of T1/2 N+ tumors (2). After neoadjuvant systemic treatment followed by mastectomy, radiotherapy was administered in cases with risk factors (2). Irradiation of supra-/infraclavicular lymph nodes with or without internal mammary lymph nodes [depending on estimated heart and

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lung toxicity (10-12)] was performed in the case of involvement of more than three axillary lymph nodes and involvement of three or fewer with risk factors. When the treatment volume included lymph nodes, the preferred radiation regimen was 28x1.8 Gy (2).

The patients were evaluated for sleep disorders prior to the start of radiotherapy (no vs. yes) to obtain the corresponding prevalence. In addition, 23 patient and tumor characteristics were investigated for potential associations with the occurrence of sleep disorders prior to radiotherapy (Table I). These characteristics included age ( $\leq 64$  vs.  $\geq 65$  years); Karnofsky performance score (90-100 vs. 60-80); Charlson comorbidity index (2-3 vs.  $\geq 4$ ); previous or concurrent additional breast cancer or ductal carcinoma *in situ* (DCIS) (no vs. yes); previous or concurrent additional tumor (no vs. yes); family history of malignancy in general (no vs. yes); family history of breast cancer or DCIS (no vs. yes); previous radiotherapy (no vs. yes); distress score (0-4 vs.  $\geq 5$ ; median=4) according to the National Comprehensive Cancer Network Distress Thermometer (8; 9); number of emotional (0-1 vs.  $\geq 2$ , median=1), physical (0-3 vs.  $\geq 4$ , median=3) or practical (0 vs.  $\geq 1$ , median=0) problems according to the Distress Thermometer; request for psycho-oncological support (no vs. yes); tumor type (DCIS vs. invasive breast cancer); type of surgery (breast conserving surgery vs. mastectomy); chemotherapy prior to radiotherapy (no vs. yes) and treatment volume of radiotherapy (breast/chest wall vs. breast/chest wall plus regional lymph nodes). In patients with invasive cancer, additional characteristics were investigated including primary tumor stage (T1-2 vs. T3-4), nodal stage (N0-1mi vs. N1-3), distant metastasis (no=M0 vs. yes=M1), histology (no special type vs. other histology), histological grading (1-2 vs. 3) and triple (estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2)/neu-status) negativity (no vs. yes). The statistical analyses regarding the potential associations between these characteristics and sleep disorders prior to radiotherapy were performed with the chi-square test (Fisher's exact test was used in case of  $n < 5$ ). *p*-Values less than 0.05 were considered as indicating significance and *p*-values under 0.07 as indicating a trend.

## Results

In the entire cohort of 175 patients, 78 patients (44.6%) stated they had a sleep disorder prior to the start of radiotherapy. Occurrence of sleep disorders was significantly associated with higher distress score ( $p < 0.0001$ ); a greater number of emotional ( $p < 0.0001$ ), physical ( $p < 0.0001$ ) or practical problems ( $p < 0.001$ ); and request for psycho-oncological support ( $p < 0.001$ ). In addition, trends were found for lower Karnofsky performance score ( $p = 0.062$ ), and higher Charlson comorbidity index ( $p = 0.059$ ). The results of the complete analysis are summarized in Table II.

## Discussion

Both non-metastatic and metastatic breast cancer are common situations in the field of radiation oncology (13-18). The majority of patients with breast cancer have non-metastatic disease and receive surgery followed by adjuvant radiotherapy (2). To be assigned to radiotherapy may cause

patients certain fears that can lead to stressful sleep disorders. In the study of Garrett *et al.* that compared 78 patients with breast cancer to 82 with prostate cancer, the rates of fatigue ( $p = 0.03$ ) and sleep disorders ( $p < 0.0001$ ) were significantly higher in the breast cancer group (3). Moreover, patients with breast cancer reported significantly higher levels of fatigue ( $p = 0.005$ ) and sleep disturbance ( $p = 0.008$ ). However, when using wrist actigraphy, sleep quality was actually better in the breast cancer group ( $p = 0.02$ ). Besides the type of cancer, the point in time of sleep disorders in patients receiving radiotherapy is an important issue. The study of Thomas *et al.* investigated changes in sleep quality in patients with breast cancer ( $n = 33$ ) and prostate cancer ( $n = 23$ ), during a radiotherapy course and up to 6 months afterwards (4). Patients of both groups reported that they experienced most sleep disorders prior to and at the beginning of their radiotherapy course. Coping strategies had a significant impact on sleep trajectories in both groups. Approach coping was associated with improved sleep quality in those with prostate cancer, and avoidance coping was associated with poorest sleep quality in both groups. On the contrary, in a population-based epidemiological study including 465 patients with breast cancer and 263 with prostate cancer, insomnia increased during the course of treatment due to the side-effects of anticancer therapy including radiotherapy (5). In general, little is known about the sleep quality of cancer patients prior to and during a course of radiotherapy.

The present study was performed to determine the prevalence of sleep disorders prior to the start of radiotherapy in a cohort of patients with breast cancer. Another major goal was the identification of significant risk factors. The prevalence of pre-radiotherapy sleep disorders was 44.6%. This rate was similar to the rate of 48% found in the previous study of Savard *et al.* that was performed on 300 patients with non-metastatic breast cancer (6). Other previous studies observed higher rates (about 60%) of sleep disorders in patients with breast cancer treated with radiotherapy (19, 20). However, these rates were assessed at 1 year following radiotherapy and not prior to or during the treatment. Therefore, these figures cannot be compared to the rates found in the study of Savard *et al.* (6) and in the present study. In another study that did not focus on patients with breast cancer but also included patients with prostate cancer, lung cancer and brain tumors, 57% of patients reported sleep disorders at initiation of radiotherapy (21).

In the current study, several characteristics were significantly associated or showed a trend for an association with the occurrence of sleep disorders prior to the start of radiotherapy and, therefore, can be considered risk factors. These characteristics included worse performance status, higher comorbidity index, higher distress score, request for

Table I. Distribution of patient and tumor characteristics investigated for associations with sleep disorders prior to the start of radiotherapy in the entire cohort.

Factor	Subgroup	Frequency, n (%)
Age	≤64 Years	93 (53.1)
	≥65 Years	82 (46.9)
Karnofsky performance score	90-100	143 (81.7)
	60-80	32 (18.3)
Charlson comorbidity index	2-3	149 (85.1)
	≥4	26 (14.9)
Additional breast cancer/DCIS	No	161 (92)
	Yes	14 (8)
History of additional tumor	No	156 (89.1)
	Yes	19 (10.9)
Family history of malignancy	No	63 (36)
	Yes	112 (64)
Family history of breast cancer/DCIS	No	116 (66.3)
	Yes	59 (33.7)
Previous radiotherapy	No	160 (91.4)
	Yes	15 (8.6)
Distress score	0-4	89 (50.9)
	≥5	86 (49.1)
Number of emotional problems	0-1	93 (53.1)
	≥2	82 (46.9)
Number of physical problems	0-3	96 (54.9)
	≥4	79 (45.1)
Number of practical problems	0	131 (74.9)
	≥1	44 (25.1)
Request for psycho-oncological support	No	142 (81.1)
	Yes	33 (18.9)
Tumor type	DCIS	17 (9.7)
	Invasive cancer	158 (90.3)
Type of surgery	BCS	154 (88)
	Mastectomy	21 (12)
Chemotherapy pre-RT	No	110 (62.9)
	Yes	65 (37.1)
Treatment volume of RT	Without LN	138 (78.9)
	With LN	37 (21.1)
Primary tumor stage*	T1-2	142 (89.9)
	T3-4	16 (10.1)
Nodal stage*	N0-1mi	112 (70.9)
	N1-3	46 (29.1)
Distant metastasis*	No	156 (98.7)
	Yes	2 (1.3)
Histology*	NST	135 (85.4)
	Other	23 (14.6)
Histologic grading*	1-2	107 (67.7)
	3	51 (32.3)
Triple negative tumor*	No	144 (91.1)
	Yes	14 (8.9)

BCS: Breast-conserving surgery; DCIS: ductal carcinoma *in situ*; LN: lymph nodes; NST: no special type; RT: radiotherapy. \*Invasive cancer only (n=158).

psycho-oncological support, and greater numbers of emotional, physical or practical problems. In the study of Dhruva *et al.* that investigated sleep disturbance prior to, during and after radiotherapy in 73 patients with breast cancer, comorbidity, evening fatigue and depressive symptoms were associated with subjective sleep disturbance

at baseline (7). In the study including different types of malignancy, mood disturbances were associated with a higher rate of sleep disorders (21). The results of our present study agree well with these findings. In addition to the previously reported characteristics, our study also identified physical and practical problems as significant risk factors for

Table II. Associations of patient and tumor characteristics with sleep disorders prior to the start of radiotherapy.

Factor		Sleep disorder, n (%)		p-Value
		Yes	No	
Age	≤64 Years	43 (55.1)	50 (51.5)	0.64
	≥65 Years	35 (44.9)	47 (48.5)	
Karnofsky performance score	90-100	59 (75.6)	84 (86.6)	0.062
	60-80	19 (24.4)	13 (13.4)	
Charlson comorbidity index	2-3	62 (79.5)	87 (89.7)	0.059
	≥4	16 (20.5)	10 (10.3)	
Additional breast cancer/DCIS	No	69 (88.5)	92 (94.8)	0.12
	Yes	9 (11.5)	5 (5.2)	
History of additional tumor	No	72 (92.3)	84 (86.6)	0.23
	Yes	6 (7.7)	13 (13.4)	
Family history of malignancy	No	24 (30.8)	39 (40.2)	0.20
	Yes	54 (69.2)	58 (59.8)	
Family history of breast cancer/DCIS	No	51 (65.4)	65 (67)	0.82
	Yes	27 (34.6)	32 (33)	
Previous radiotherapy	No	70 (89.7)	90 (92.8)	0.48
	Yes	8 (10.3)	7 (7.2)	
Distress-score	0-4	26 (33.3)	63 (64.9)	<b>&lt;0.0001</b>
	≥5	52 (66.7)	34 (35.1)	
Number of emotional problems	0-1	25 (32.1)	68 (70.1)	<b>&lt;0.0001</b>
	≥2	53 (67.9)	29 (29.9)	
Number of physical problems	0-3	21 (26.9)	75 (77.3)	<b>&lt;0.0001</b>
	≥4	57 (73.1)	22 (22.7)	
Number of practical problems	0	49 (62.8)	82 (84.5)	<b>&lt;0.001</b>
	≥1	29 (37.2)	15 (15.5)	
Request for psycho-oncological support	No	54 (69.2)	88 (90.7)	<b>&lt;0.001</b>
	Yes	24 (30.8)	9 (9.3)	
Tumor type	DCIS	4 (5.1)	13 (13.4)	0.08
	Invasive cancer	74 (94.9)	84 (86.6)	
Type of surgery	BCS	71 (91.0)	83 (85.6)	0.27
	Mastectomy	7 (9.0)	14 (14.4)	
Chemotherapy pre-RT	No	44 (56.4)	66 (68.0)	0.11
	Yes	34 (43.6)	31 (32.0)	
Treatment volume of RT	Without LN	60 (76.9)	78 (80.4)	0.57
	With LN	18 (23.1)	19 (19.6)	
Primary tumor stage*	T1-2	69 (93.2)	73 (86.9)	0.19
	T3-4	5 (6.8)	11 (13.1)	
Nodal stage*	N0-1mi	53 (71.6)	59 (70.2)	0.85
	N1-3	21 (28.4)	25 (29.8)	
Distant metastasis*	No	72 (97.3)	84 (100)	0.22
	Yes	2 (2.7)	0 (0)	
Histology*	NST	67 (90.5)	68 (81.0)	0.09
	Other	7 (9.5)	16 (19.0)	
Histologic grading*	G1-2	48 (64.9)	59 (70.2)	0.47
	G3	26 (35.1)	25 (29.8)	
Triple negative tumor*	No	68 (91.9)	76 (90.5)	0.75
	Yes	6 (8.1)	8 (9.5)	

BCS: Breast-conserving surgery; DCIS: ductal carcinoma *in situ*; LN: lymph nodes; NST: no special type; RT: radiotherapy. \*Invasive cancer only (n=158). Statistically significant p-Values are shown in bold.

sleep disorders. When interpreting the results of this study, its retrospective nature should be considered, which bears the risk of hidden selection biases. However, these results are important for the design of a prospective trial that will investigate sleep disorders in patients with breast cancer,

prior to and during a course of radiotherapy. A particular focus of this trial will be on the impact of the use of smartphones and tablets at bedtime on sleep quality.

In conclusion, pre-treatment sleep disorders are common in patients with breast cancer assigned to radiotherapy. This

applies particularly to patients with risk factors such as worse performance status, higher comorbidity index and distress including emotional, physical or practical problems. These patients should be offered psycho-oncological support as soon as possible, ideally during their first contact with a radiation oncologist.

### 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.T. and T.W.K. participated in the design of the study. D.R., C.A.N. and L.D. provided data. D.R. performed the analyses and interpretation of the data. D.R., S.T. and T.W.K. drafted the article, which was reviewed and finally approved by all Authors.

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