

Frequency and Risk Factors of Sleep Disturbances in Patients With Prostate Cancer Assigned to Local or Loco-regional Radiotherapy

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Abstract. *Background/Aim:* Many patients with prostate cancer receive definitive or adjuvant radiotherapy. This study aimed to identify the frequency of sleep disturbances and corresponding risk factors prior to radiation treatment. *Patients and Methods:* Data of 48 patients assigned to local or loco-regional irradiation for prostate cancer were retrospectively analyzed for pre-radiotherapy sleep disturbances. Fifteen characteristics were analyzed including age, performance status, comorbidity, history of previous malignancy, distress score, (emotional, physical or practical) problems, prostate-specific antigen, primary tumor stage, Gleason-score, upfront androgen deprivation therapy (ADT), treatment volume, brachytherapy, and COVID-19 pandemic. *Results:* Pre-radiotherapy sleep disturbances were reported by 20.8% of patients and significantly associated with distress scores ≥ 4 ($p < 0.0001$) and ≥ 3 physical problems ($p = 0.0001$). Trends were found for Karnofsky performance score ≤ 80 ($p = 0.095$), Gleason score 7b-9 ($p = 0.079$), and ADT ($p = 0.067$). *Conclusion:* Pre-radiotherapy sleep disturbances were less common in prostate cancer patients than in other cancer patients. Risk factors were identified that can help identify patients requiring psychological support prior to radiotherapy.

Prostate cancer represents the most common malignancy in men (1). Many patients with prostate cancer are treated with

local or loco-regional irradiation, either with external beam radiotherapy (EBRT) alone, EBRT plus brachytherapy or brachytherapy alone. To be assigned only to radiation treatment may cause significant emotional distress including fear about the unknown technology, exposure to radiation, and possible side effects of the planned treatment (2-6). Emotional distress may lead to burdensome sleep disturbances.

In the study of Thomas *et al.* that included 23 patients (41%) irradiated for prostate cancer, patients reported sleep disturbances mostly prior to and during early weeks of radiotherapy (7). Moreover, in the prospective study of Holliday *et al.* that investigated 28 men irradiated for early-stage prostate cancer, sleep efficiency improved and sleep-onset latency decreased during the course of treatment (8).

However, only very limited data are available regarding sleep disturbances in patients just before receiving local or loco-regional radiotherapy for prostate cancer. Therefore, we performed this study, mainly to provide data regarding the frequency and potential risk factors of pre-radiotherapy sleep disturbances in this group of patients. Knowledge of risk factors can help identify patients who would benefit from psychological support already before the beginning of their radiotherapy course.

Patients and Methods

Data of 48 patients receiving local or loco-regional irradiation for prostate cancer, who completed a National Comprehensive Cancer Network Distress Thermometer evaluation prior to the start of treatment (9, 10) were retrospectively analyzed for sleep disturbances. The study was approved by the responsible Ethics Committee (University of Lübeck, reference 21-284).

Forty-three of the 48 patients were assigned to definitive radiation treatment. Thirty-six of these patients were scheduled for 50 Gy of EBRT (5x2.0 Gy per week) to the prostate plus/minus

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Key Words: Prostate cancer, external beam radiotherapy, brachytherapy, sleep disturbances, frequency, risk factors.

seminal vesicles and safety margins of 12-15 mm to be followed by a boost to the prostate. One patient refused the treatment. Of the remaining 35 patients, 23 patients received an EBRT-boost (safety margins of 5 mm) of 24-28 Gy and 12 patients a brachytherapy boost (high-dose rate) with two weekly fractions of 15 Gy. Six of the 43 patients were assigned to irradiation of the prostate plus loco-regional lymph nodes, and one patient to irradiation of the prostate plus pelvic and femoral bone metastases.

Five of the 48 patients were scheduled for adjuvant EBRT with 66-70 Gy (5x2.0 Gy per fraction) of the prostatic fossa following microscopically incomplete resection. In the entire cohort, 13 patients had received androgen deprivation therapy (ADT) with bicalutamide and/or leuprorelin-acetate prior to the start of their radiotherapy course.

Sleep disturbances were evaluated prior to the radiotherapy course. Fifteen patient and tumor characteristics were analyzed for potential associations with the occurrence of sleep disturbances (Table I). The characteristics included age at the time of evaluation of sleep disturbances (≤ 72 vs. ≥ 73 years, median=72 years), Karnofsky performance score (≤ 80 vs. >80), Charlson comorbidity index (≤ 5 vs. ≥ 6 , median=5), history of previous malignancy (no vs. yes), distress score (≤ 3 vs. ≥ 4 ; median=3) assessed with the National Comprehensive Cancer Network Distress Thermometer (9, 10), emotional problems (no vs. yes), number of physical problems (0-2 vs. ≥ 3 , median=2), practical problems (no vs. yes), prostate-specific antigen (PSA) level (≤ 10 vs. >10 ng/ml), primary tumor stage (T1 vs. T2-3), Gleason-score (5-7a vs. 7b-9), ADT prior to radiotherapy (no vs. yes), treatment volume of radiotherapy (prostatic region only vs. prostatic region plus loco-regional lymph nodes), brachytherapy boost (no vs. yes), and relation to COVID-19 pandemic (before vs. during the pandemic). The International Prostate Symptom Score (IPSS) was not evaluated, since general assessment of urinary symptoms/problems is included in the National Comprehensive Cancer Network Distress Thermometer (9, 10).

Statistical analyses of potential associations between the 15 investigated characteristics and sleep disturbances were performed with the Fisher's exact test and the chi-square test (in case of $n \geq 5$). *p*-Values of less than 0.05 were regarded significant, and *p*-values < 0.10 were considered indicating a trend.

Results

Pre-radiotherapy sleep disturbances were reported by 10 of 48 patients, representing a prevalence of 20.8%. The occurrence of sleep disturbances was significantly associated with a higher distress score (≥ 4 vs. ≤ 3 , $p < 0.0001$) and a greater number of physical problems (≥ 3 vs. 0-2, $p = 0.0001$). In addition, trends were found for a lower Karnofsky performance score (≤ 80 vs. >80 , $p = 0.095$), a higher Gleason score (7b-9 vs. 5-7a, $p = 0.079$), and ADT prior to radiotherapy (yes vs. no, $p = 0.067$). In contrast, the COVID-19 pandemic had no impact on the occurrence of sleep disturbances ($p > 0.999$). The results of all patient and tumor characteristics are shown in Table II.

Discussion

Many patients with prostate cancer are candidates for definitive or adjuvant radiotherapy. The anticipation of

Table I. Patient and tumor characteristics.

Characteristic	Subgroup	Frequency, n (%)
Age	≤ 72 Years	25 (52)
	≥ 73 Years	23 (48)
Karnofsky performance score	≤ 80	6 (13)
	>80	42 (87)
Charlson comorbidity index	≤ 5	29 (60)
	≥ 6	19 (40)
History of previous malignancy	No	40 (83)
	Yes	8 (17)
Distress score	≤ 3	28 (58)
	≥ 4	20 (42)
Emotional problems	No	25 (52)
	Yes	23 (48)
Number of physical problems	0-2	27 (56)
	≥ 3	21 (44)
Practical problems	No	43 (90)
	Yes	5 (10)
PSA level prior to RT	≤ 10 ng/ml	21 (44)
	>10 ng/ml	23 (48)
	Unknown	4 (8)
Primary tumor stage	T1	37 (77)
	T2-3	10 (21)
	Unknown	1 (2)
Gleason Score	5-7a	22 (46)
	7b-9	25 (52)
	Unknown	1 (2)
ADT prior to RT	No	35 (73)
	Yes	13 (27)
Treatment volume of RT	Prostatic region only	41 (85)
	Prostatic region plus LN*	7 (15)
Brachytherapy boost	No	35 (73)
	Yes	13 (27)
COVID-19 pandemic	Before	28 (58)
	During	20 (42)

PSA: Prostate-specific antigen; RT: radiotherapy; ADT: androgen deprivation therapy; LN: lymph nodes (*one patient with pelvic and femoral bone metastases instead of LN); COVID-19: Coronavirus Disease 2019.

radiation treatment may lead to sleep disturbances as a consequence of distress and fear regarding the unknown modern technology, exposure to radiation, and treatment-associated toxicity (2-6).

Since only few studies are available that evaluated the frequency of sleep disturbances in patients locally or loco-regionally irradiated for prostate cancer and corresponding risk factors, the present study was conducted. In our study, which focused on pre-radiotherapy sleep disturbances, the frequency of these sleep problems was 20.8%. This frequency is similar to the 25.6% found by Garrett *et al.* when they used the General Sleep Disturbance Scale (GSDS) for assessment of pre-radiotherapy sleep disturbances (11). Moreover, the frequency of 20.8% in the present study was

Table II. Associations of patient and tumor characteristics with pre-radiotherapy sleep disorders.

Characteristic		Sleep disorders, n (%)		p-Value
		Yes (n=10)	No (n=38)	
Age	≤72 Years	6 (60)	19 (50)	0.727
	≥73 Years	4 (40)	19 (50)	
Karnofsky performance score	≤80	3 (30)	3 (8)	0.095
	>80	7 (70)	35 (92)	
Charlson comorbidity index	≤5	5 (50)	24 (63)	0.449
	≥6	5 (50)	14 (37)	
History of previous malignancy	No	8 (80)	32 (84)	0.666
	Yes	2 (20)	6 (16)	
Distress-score	≤3	0 (0)	28 (74)	<0.0001
	≥4	10 (100)	10 (26)	
Emotional problems	No	3 (30)	22 (58)	0.162
	Yes	7 (70)	16 (42)	
Number of physical problems	0-2	0 (0)	27 (71)	0.0001
	≥3	10 (100)	11 (29)	
Practical problems	No	9 (90)	34 (89)	>0.999
	Yes	1 (10)	4 (11)	
PSA level prior to RT	≤10 ng/ml	4 (44)	17 (49)	>0.999
	>10 ng/ml	5 (56)	18 (51)	
Primary tumor stage	T1	9 (90)	28 (76)	0.665
	T2-3	1 (10)	9 (24)	
Gleason Score	5-7a	2 (20)	20 (54)	0.079
	7b-9	8 (80)	17 (46)	
ADT prior to RT	No	5 (50)	30 (79)	0.067
	Yes	5 (50)	8 (21)	
Treatment volume of RT	Prostatic region only	8 (80)	33 (87)	0.625
	Prostatic region plus LN*	2 (20)	5 (13)	
Brachytherapy	No	7 (70)	28 (74)	>0.999
	Yes	3 (30)	10 (26)	
COVID-19 pandemic	Before	6 (60)	22 (58)	>0.999
	During	4 (40)	16 (42)	

PSA: Prostate-specific antigen; RT: radiotherapy; ADT: androgen deprivation therapy; LN: lymph nodes (*one patient with pelvic and femoral bone metastases instead of LN); COVID-19: Coronavirus Disease 2019. Statistically significant *p*-values are shown in bold.

in the range of 19-39% reported by prostate cancer patients in different situations including prior to curative surgery or following treatment for prostate cancer (12-15).

Another major goal of the present study was the identification of prognostic factors predicting a higher risk of pre-radiotherapy sleep disturbances. The occurrence of these sleep problems was significantly associated with a higher distress score and a greater number of physical problems. In addition, trends for associations with pre-radiotherapy sleep disturbances were found for a worse performance status, a higher Gleason score, and administration of ADT prior to the radiation treatment.

These results were in line with those of previous studies of patients with prostate cancer that did not focus on pre-radiotherapy sleep disturbances. In the studies of Maguire *et al.* and Savard *et al.*, symptoms of depression and anxiety that can be considered indicators of distress were positively associated with sleep disturbances in patients with prostate

cancer (15, 16). In these studies, sleep disturbances were significantly associated with gastrointestinal symptoms, genitourinary symptoms, and pain that are rated as physical problems in the National Comprehensive Cancer Network Distress Thermometer (9, 10). In the trial of Wiggins *et al.*, patients with more pronounced sleep problems had a higher IPSS and were more likely to have nocturia ($p < 0.001$), which both can be considered physical problems (17). In a longitudinal study of Savard *et al.*, sleep problems were associated with urinary symptoms and pain (18). In addition, a previous study found an association between sleep disturbances and a higher Gleason score (17), and several studies reported associations between sleep disturbances and ADT (15, 16, 18-20).

Moreover, in previous studies of our group, in which pre-radiotherapy sleep disturbances were investigated in patients with other primary tumor types and the same approach was used as in the present study, sleep problems were also

associated with higher scores, more physical problems, more aggressive or advanced tumors, and hormonal therapy (21-24). Thus, the findings of the present study can be considered consistent with the results of previous studies evaluating sleep disturbances in patients with prostate cancer in different situations and in prior to a radiotherapy course in patients with prostate cancer or other types of primary tumor (15-24). However, the limitations of the current study, namely its retrospective design with the risk of hidden selection biases and its comparably small sample size should be considered when interpreting the results.

In conclusion, the frequency of pre-radiotherapy sleep disturbances was 20.8% and less common than in patients with other cancer types (21-24). The occurrence of sleep disturbances was associated with several risk factors. These factors can be helpful when aiming to identify patients who will likely benefit from psychological support prior to the start of radiotherapy.

Conflicts of Interest

The Authors state that there are no conflicts of interest related to this study.

Authors' Contributions

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

Acknowledgements

As part of the project NorDigHealth, this study is funded by the European Regional Development Fund through the Interreg Deutschland-Danmark program.

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Received August 13, 2021

Revised August 28, 2021

Accepted September 1, 2021