ANTICANCER RESEARCH *42*: 3085-3089 (2022)
doi:10.21873/anticanres.15796

Improvement of Sleep Disorders During a Course of Radiotherapy for Breast Cancer – Final Results of the Prospective Interventional RADIO-SLEEP Trial

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Abstract. *Background/Aim: Upcoming radiotherapy may cause distress and sleep disorders (SDO). This prospective interventional trial investigated SDO during a course of radiotherapy for breast cancer. Patients and Methods: Fifty patients were eligible. The primary endpoint was improvement of SDO after 15 fractions. Additional endpoints included SDO after 5 fractions and at the end of radiotherapy (EOT). Additional characteristics were analysed including use of smartphones/tablets, age, body mass index, performance score, comorbidity score, surgery, distress score, and emotional/physical/practical problems. Results: After 15 fractions, 38% of patients reported improvement of SDO (p<0.0001). Improvement rates were 22% after 5 fractions (p=0.003) and 39% at EOT (p<0.0001). Moreover, a significant association was observed for lower distress score after 5 fractions. Conclusion: Improvement of SDO occurred more often than expected, most likely due to habituation to radiotherapy. Since SDO did not improve in the majority of patients, timely psychological support should be offered to all patients.*

The vast majority of patients with non-metastatic breast cancer are treated with adjuvant local or loco-regional irradiation. Merely to be scheduled for a course of radiotherapy may lead to emotional distress which can result in burdensome sleep disorders (SDO). SDO prior to radiotherapy for breast cancer were reported in almost 50% of patients (1, 2). One important question is whether the rate of SDO during a course of radiotherapy decreases, increases or remains unchanged. The very few available studies addressing this question have produced conflicting results (3, 4). A prospective study of 33 breast cancer and 23 prostate cancer patients investigated coping processes during the course of radiotherapy and up to 6 months afterwards (3). The majority of patients reported the maximum of their SDO prior to the start and during the initial fractions of the radiotherapy course. In contrast, in a study including 465 breast cancer patients who were part of a population-based epidemiological study, side effects of radiotherapy led to aggravation of insomnia symptoms (4). Thus, additional studies are required that evaluate the course of SDO during a series of radiation treatment. In case of increase of SDO, patients may need early psycho-oncological support. The prospect of improvement of SDO during the course of radiotherapy would likely reassure the patients and reduce potential distress. Therefore, this prospective trial was conducted to investigate the course of SDO during adjuvant radiotherapy in breast cancer patients.

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Key Words: Breast cancer, adjuvant radiotherapy, sleep disorders, prospective trial, patient reported outcomes.

Patients and Methods

Patient selection. This prospective single-center trial investigated the course of SDO during adjuvant radiotherapy in patients with breast cancer. The trial was approved by the responsible ethics committee (University of Lübeck, reference 21-137), registered at clinicaltrials.gov (NCT04879264), and performed in accordance with the Declaration of Helsinki. Criteria for inclusion and exclusion were previously reported (5). Fifty-two patients were enrolled, and 50 patients were eligible for the full analysis set. In one patient, symptomatic leptomeningeal carcinomatosis was

identified during the initial phase of radiotherapy, local radiotherapy was discontinued, and palliative treatment was initiated. In another patient, doses per fraction were changed to 3.0 Gy due to advanced age and poor performance status.

Radiotherapy. Of the 50 patients included in the full analysis set, 44 patients (88%) were treated with breast conserving surgery (BCS). Thirty-five of these patients (70%) received 15×2.667 Gy to the whole breast, which was followed by a sequential boost of 5×2 Gy to the tumor bed in 23 patients. An additional nine patients (18%) received 28×1.8 Gy to the whole breast and loco-regional lymph nodes, followed by a boost of 5×2 Gy to the tumor bed in six patients. Of the six patients (12%) treated with mastectomy, one patient (2%) received 15×2.667 Gy to the thoracic wall, and five patients (10%) 28×1.8 Gy to the thoracic wall and loco-regional lymph nodes. A boost was not given in patients treated with mastectomy. Radiotherapy was performed as intensity-modulated radiation therapy (IMRT) in 42 patients (84%) and as volumetric modulated arc therapy (VMAT) in eight patients (16%).

Endpoints and assessments. The primary endpoint was the rate of improvement of SDO after 15 fractions of radiotherapy compared to baseline prior to the start of radiotherapy. Improvement of SDO was defined as decrease of severity of SDO by at least 2 points on a patient self-rating scale (0=no problems; 10=maximum problems) and/or decrease of distress due to SDO by at least 2 points on a patient self-rating scale (0=no distress; 10=maximum distress) and/or reduction of sleeping drug dose(s) by at least 25%. Patients must have had at least 2 points on one of the self-rating scales at baseline. Additional endpoints included SDO after 5 fractions and at the end of radiotherapy (EOT). Moreover, several characteristics were assessed at baseline and analyzed including the use of smartphones or tablets (more rarely *vs*. more extensively), age at radiotherapy (≤60 *vs*. >60 years, median=60 years), body mass index (≤25 *vs*. >25, median=25), Eastern Cooperative Oncology Group performance score (0 *vs*. 1-2, median=0), age-adjusted Charlson comorbidity score (≤4 *vs*. >4, median=4), type of breast surgery (BCS vs mastectomy), distress score (6) (≤6 *vs*. >6, median=6), number of emotional problems (≤2 *vs*. >2, median=2), number of physical problems (≤5 *vs*. >5, median=5), and practical problems (no *vs*. yes) (Table I). Patients with smartphones or tablets completed a questionnaire regarding frequency and time using these devices, which resulted in a score between 0 (very rare use) and 10 (very extensive use) points. More rare use was defined as ≤2.0 points and more extensive use as ≥2.5 points (median=2.25 points).

Statistical analysis. According to sample size calculations, at least 51 patients should be enrolled and at least 48 patients should be available for the full analysis set. Due to uncertainty regarding eligibility of one patient, a total of 52 patients were enrolled. Details of the sample size calculations were already reported (5). Improvement rates of SDO of 25% and 28% after 15 fractions would have resulted in a statistical power of 80% and 90%, respectively (one-sided exact test for one binomial population, significance level=2.5%). Rates of improvement of sleep disorders after 5 fractions, after 15 fractions (main endpoint) and at the end of radiotherapy, respectively, were compared to SDO at baseline using the Fisher's exact test. *p*-Values <0.05 were considered significant. The statistical analyses were performed with SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

After 15 fractions, 19 of 50 patients (38%) showed improvement of their SDO ($p<0.0001$; one-sided binomial test to test whether the rate of improved SDO is significantly larger than 10%). Improvement rates were 22% (10 of 45 evaluable patients) after 5 fractions of radiotherapy ($p=0.003$) and 39% (19 of 49 evaluable patients) at EOT ($p<0.0001$). Of the investigated characteristics at the three time points, a significant association with improvement of SDO was observed only for a lower overall distress score (≤6) after 5 fractions (Table I). The descriptive analyses of changes from baseline of the severity of SDO, distress caused by SDO and dose reduction of sleeping drugs are shown in Table II. Deterioration (increase) of SDO after 5 fractions, after 15 fractions and at EOT occurred in 6 of 45 patients (13%), 6 of 50 patients (12%) and 8 of 49 patients (16%), respectively. SDO did not significantly change in 29 (64%), 25 (50%) and 22 patients (45%), respectively.

Discussion

SDO may be a consequence of emotional distress caused by upcoming anti-cancer treatment (7). Several studies reported the prevalence of pre-radiotherapy SDO for various tumor entities. In breast cancer patients, the prevalence of SDO prior to the start of radiotherapy ranged between 38% and 48% (1, 2, 8, 9). This prevalence was higher than in prostate cancer patients (21%) and similar to patients with lung cancers (40-45%), head-and-neck cancers (37-43%), gynecological cancers (44-47%), and colorectal cancers (30-43%) (9-15).

Only a few studies have focused on SDO in breast cancer patients scheduled for adjuvant radiotherapy. Moreover, these studies produced conflicting results regarding the course of SDO during the series of radiotherapy. In the prospective study of Thomas *et al*. that included breast cancer and prostate cancer patients, SDO were more prominent prior to and at the beginning of the radiotherapy course (3). Breast cancer patients reported that they had more SDO, particularly difficulties to fall asleep, prior to the radiotherapy course and that their SDO showed gradual improvement during the course of treatment. In contrast, Savard *et al*. reported aggravation of insomnia during a course of radiotherapy in a cohort of breast cancer and prostate cancer patients (4). In the breast cancer patients, SDO were significantly mediated by acute radiation-related side effects ($p<0.01$). In a randomized trial that investigated the effect of physical exercise on SDO in breast cancer patients, SDO slightly increased in the control ("relaxation") group during the radiotherapy course (16). In the study of Dhruva *et al*., SDO were assessed objectively with the Wake After Sleep Onset (WASO) and subjectively (patients' impression) with the General Sleep Disturbance Scale (GSDS) in 73 patients irradiated for breast cancer (17).

Table I. *Rates of improvement of sleep disorders (compared to baseline) after 5 fractions, after 15 fractions (main endpoint) and at the end of radiotherapy. p-Values were calculated with Fisher's exact test.*

Characteristic	After 5 fractions % (n of N patients)	After 15 fractions % (n of N patients)	End of radiotherapy % (n of N patients)
Use of smartphones/tablets	*p*=0.73	*p*=1.00	*p*=0.77
More rarely	19 (4/21)	40 (10/25)	42 (10/24)
More extensively	25 (6/24)	36 (9/25)	36 (9/25)
Age at radiotherapy	*p*=1.00	*p*=1.00	*p*=1.00
≤60 years	23 (6/26)	37 (10/27)	37 (10/27)
>60 years	21 (4/19)	39 (9/23)	41 (9/22)
Body mass index	*p*=0.08	*p*=0.56	*p*=0.56
≤25	10 (2/21)	32 (8/25)	33 (8/24)
>25	33 (8/24)	44 (11/25)	44 (11/25)
ECOG performance score	*p*=0.32	*p*=1.00	*p*=1.00
0	21 (8/39)	40 (17/43)	40 (17/42)
1-2	40 (2/5)	33 (2/6)	33 (2/6)
Age-adjusted Charlson score	*p*=1.00	*p*=0.55	*p*=0.14
≤4	24 (7/29)	33 (10/30)	30 (9/30)
>4	19 (3/16)	45 (9/20)	53 (10/19)
Type of breast surgery	*p*=1.00	*p*=1.00	*p*=0.66
Breast conserving surgery	22 (9/41)	39 (17/44)	37 (16/43)
Mastectomy	25 (1/4)	33 (2/6)	50 (3/6)
Overall distress score (6)	*p*=0.006	*p*=0.55	*p*=1.00
≤6	36 (9/25)	43 (12/28)	36 (10/28)
>6	0 (0/18)	30 (6/20)	37 (7/19)
Number of emotional problems	*p*=0.44	*p*=0.76	*p*=0.75
≤2	23 (5/22)	41 (11/27)	37 (10/27)
>2	12 (2/17)	35 (6/17)	31 (5/16)
Number of physical problems	*p*=0.70	*p*=0.36	*p*=1.00
≤5	24 (5/21)	46 (11/24)	38 (9/24)
>5	16 (3/19)	29 (6/21)	35 (7/20)
Practical problems	*p*=0.65	*p*=1.00	*p*=1.00
No	10 (1/10)	36 (4/11)	40 (4/10)
Yes	23 (7/30)	38 (13/34)	35 (12/34)

Table II. *Descriptive analyses of changes from baseline of the severity of sleep disorders, distress caused by sleep disorders and dose reduction of sleeping drugs.*

	After 5 fractions	After 15 fractions	End of radiotherapy
Severity of sleep disorder [n (%)]			
No decrease by ≥2 points	36 (80)	36 (72)	33 (77)
Decrease by ≥2 points	9 (20)	14 (28)	10 (23)
Distress sleep disorder [n (%)]			
No decrease by ≥2 points	39 (87)	36 (72)	32 (74)
Decrease by ≥2 points	6 (13)	14 (28)	11 (26)
Dose reduction of sleeping drugs [n (%)]			
No	44 (98)	48 (96)	41 (98)
Yes	1 (2)	2 (4)	1 (2)

The objective SDO increased slightly during the course of radiotherapy, whereas the subjective SDO showed a slight decrease. The trajectory of subjective SDO was associated with depressive symptoms.

When reviewing the available studies, we felt that the effect of habituation to radiotherapy appeared more likely, particularly since acute toxicities would be less prominent if modern radiotherapy techniques are used. Therefore, the rate

of improvement (decrease) of SDO was selected as main endpoint of the RADIO-SLEEP trial. An improvement rate of 28% after 15 fractions was assumed resulting in a statistical power of 90%. According to the results of this trial, the rate of improvement of SDO after 15 fractions was considerably higher than expected. The same accounted for the improvement rate at EOT. These findings support the results of the study of Thomas *et al*. and the hypothesis that the effect of habituation to radiotherapy on SDO is stronger than the impact of radiation-related side effects. Radiation oncologists can address this result during informed consent discussions and tell the patients with SDO that there is a chance of improvement of approximately 40% during the course of radiotherapy. However, one has to be aware that after 15 fractions SDO did not improve in 62% of the patients. Patients without improvement of SDO had significantly higher general distress scores at baseline (6). This result agrees with the findings of a retrospective study that investigated risk factors of SDO prior to radiotherapy in 338 breast cancer patients (8). Thus, particularly patients with higher distress scores could benefit from timely psychological support. However, such support should be offered to all breast cancer patients, regardless of the initial distress score. Moreover, the limitations of this study should be considered during the interpretation of its results. These include the comparably small sample size, the fact that patient self-rating scales used for this study were not validated, and the use of different dose-fractionation regimens of radiotherapy with different overall treatment times.

Conclusion

In summary, improvement of SDO during a course of adjuvant radiotherapy for breast cancer occurred more often than expected, most likely due to habituation to the procedure of radiotherapy. However, since SDO did not improve in the majority of patients, timely psychological support should be offered to all patients. These aspects should be included in consent discussions with the patients. When interpreting the results of this study, its limitations should be considered. Additional prospective trials are warranted to further evaluate the role of SDO during a course of radiotherapy for breast cancer. Moreover, future studies should investigate SDO during radiotherapy in patients with other primary tumor types.

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., C.A.N.-W., L.D., S.J., D.O., S.T. and T.W.K. participated in the study design. C.A.N.-W., L.D. and L.S. provided the data that were analyzed by a professional statistician and interpreted by all authors. D.R. and S.E.S. drafted the article, which was read and approved by all Authors.

Acknowledgements

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

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Received May 9, 2022
Revised May 19, 2022
Accepted May 20, 2022