

Emotional Problems Prior to Adjuvant Radiation Therapy for Breast Cancer

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Abstract. *Background/Aim:* Being scheduled for radiotherapy can cause emotional distress. This study aimed to identify risk factors in 338 patients assigned to radiotherapy for breast cancer. *Patients and Methods:* Nineteen potential risk factors including the COVID-19 pandemic were investigated for associations with the six emotional problems included in the National Comprehensive Cancer Network Distress Thermometer. *Results:* Worry and fears were significantly associated with age ≤ 60 years; sadness with age and Karnofsky performance score (KPS) < 90 ; depression with KPS and Charlson Comorbidity Index ≥ 3 ; loss of interest with KPS. Trends were found for associations between sadness and additional breast cancer/DCIS, Charlson Index and chemotherapy; between depression and additional breast cancer/DCIS, treatment volume and nodal stage N1-3; between nervousness and additional breast cancer/DCIS, mastectomy and triple-negativity; between loss of interest and Charlson Index, family history of breast cancer/DCIS, invasive cancer, chemotherapy, and treatment volume. The COVID-19 pandemic did not increase emotional problems. *Conclusion:* Several risk factors for emotional problems were identified. Patients with such factors should receive psychological support well before radiotherapy.

Breast cancer is the most common site of new cancers in women in many countries including Denmark and Germany (1-5). Most patients with primary breast cancer receive adjuvant radiotherapy as an integral part of breast-conserving treatment. Radiotherapy may also be indicated after mastectomy if specific risk factors exist (6). The vast majority of patients assigned to adjuvant irradiation receive external beam radiotherapy (EBRT) of the whole breast with or without a boost to the tumor bed (6). Depending on the nodal stage, the treatment volume of radiotherapy may include the locoregional lymph nodes in addition to the breast.

Being scheduled for radiotherapy and the radiation treatment itself can be associated with emotional distress. Breast cancer patients were reported to have higher prevalence and distress levels than patients with several other malignancies (7, 8). According to previous studies, 30-50% of women with breast cancer report moderate to severe distress and decline in quality of life during their course of radiation treatment (2). Moreover, higher levels of distress prior to surgery or chemotherapy for breast cancer were associated with increased adverse events during and following treatment (2). For patients receiving radiotherapy, it is important to avoid interruption of the treatment due to adverse events in order to achieve optimal results. Very few studies investigated emotional distress before a course of radiotherapy. Browall *et al.* found that better emotional functioning predicted better quality of life in patients with breast cancer receiving adjuvant radiotherapy (9). Mose *et al.* reported that 48% of patients with early-stage breast cancer were afraid of adjuvant radiotherapy after breast-conserving surgery (BCS) (10). In their study, younger age was the only significant predictor of pre-radiotherapy distress. Sohl *et al.* identified several predictors of pre-radiotherapy emotional distress including cancer stage, upfront mastectomy, response expectations and pessimism (2). Knowledge of such risk factors is important, since patients with these factors may

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experience impairment in quality of life and more pronounced radiation-related adverse events and require early psychological intervention (2, 9). Therefore, the present study investigated many patient-, tumor-, and treatment-related factors and a potential impact of the COVID-19 pandemic for associations with emotional problems prior to a course of adjuvant radiotherapy for primary breast cancer.

Patients and Methods

Data of 338 female patients with breast cancer scheduled for adjuvant treatment with external-beam radiotherapy (EBRT) were evaluated for emotional problems prior to the radiation course. This retrospective study was approved by the responsible Ethics Committee (University of Lübeck, reference 21-178). Patients included in this study had completed a questionnaire regarding distress (National Comprehensive Cancer Network Distress Thermometer) at the time of the pre-radiotherapy consent discussion with the patients (11). Of these patients who were previously evaluated for sleep disorders (12), 163 presented before and 175 patients during the COVID-19 pandemic.

Prior to radiotherapy, all patients had received surgery for their breast tumor, either as BCS (n=302) or mastectomy (n=36). Patients treated with BCS were scheduled for whole-breast irradiation (15×2.667 Gy over 3 weeks or 28×1.8 Gy over 6.5 weeks) plus/minus a boost to the tumor bed (5×2.0 Gy over 1 week) (2). Patients scheduled for radiotherapy of the chest wall after mastectomy had specific risk factors and were assigned to EBRT with 28×1.8 Gy over 6.5 weeks. Sixty-seven patients with involvement for more than three axillary lymph nodes or one to three lymph nodes plus risk factors were scheduled for EBRT of the whole breast plus locoregional lymph node regions (2).

The National Comprehensive Cancer Network Distress Thermometer (11) addresses six emotional problems, namely worry, fears, sadness, depression, nervousness and loss of interest in usual activities. Based on the patients' statements in the distress thermometer evaluation (patient reported outcomes), each problem was categorized as absent (no) or present (yes).

For each of the six emotional problems, 19 potential risk factors were investigated. These factors were relation to the COVID-19 pandemic (before vs. during), age (≤ 60 vs. ≥ 61 years, median age=60.5 years); Karnofsky performance score (KPS 90-100 vs. < 90); Charlson Comorbidity Index (2 vs. ≥ 3 , median index=2); previous or concurrent breast cancer or ductal carcinoma in situ (DCIS) (no vs. yes); previous or concurrent malignancy including breast cancer/DCIS (no vs. yes); family history of malignancy including breast cancer/DCIS (no vs. yes); family history of breast cancer/DCIS (no vs. yes); previous radiotherapy (no vs. yes); primary tumor type (DCIS only vs. invasive breast cancer with/without DCIS); type of surgery for breast tumor (BCS vs. mastectomy); preceding chemotherapy (no vs. yes), start of hormonal therapy (tamoxifen or aromatase inhibitors) before radiotherapy (no vs. yes); and volume of radiation treatment (without vs. with lymph nodes). In patients with invasive breast cancer, primary tumor (T) stage (1-2 vs. 3-4), nodal (N) stage (0-1_{mi} vs. 1-3), distant metastasis (no vs. yes), histologic grading (G) (1-2 vs. 3) and triple (estrogen receptor, progesterone receptor and status of the human epidermal growth factor receptor 2/neu) negativity (no vs. yes) were additionally evaluated.

The statistical analyses regarding associations between emotional problems and potential risk factors were performed with the chi-square test. In the case that the number of patients in a subgroup was fewer than 5, the Fisher's exact test was used. For each of the six emotional problems, separate analyses including the 19 potential risk factors were performed. When applying Bonferroni adjustment for 19 tests, *p*-Values of < 0.0026 were considered to be significant representing an alpha level of < 0.05 . *p*-Values of < 0.05 were considered as indicating a trend.

Results

The COVID-19 pandemic had no significant impact on the prevalence of emotional problems (Tables I, II, III, IV, V and VI). A total of 127 patients (38%) complained about worry prior to their radiotherapy course. Worry was significantly associated with age ≤ 60 years ($p < 0.0001$) (Table I). Fears were stated by 154 patients (46%) and were significantly associated with age ≤ 60 years ($p < 0.0001$), too (Table II).

Sadness was reported by 97 patients (29%). This emotional problem was significantly associated with age ≤ 60 years ($p = 0.0012$) and a KPS < 90 ($p = 0.0022$) (Table III). Borderline significance was found for history of previous or concurrent breast cancer/DCIS ($p = 0.0056$), and trends were observed for a Charlson Comorbidity Index ≥ 3 ($p = 0.038$) and preceding chemotherapy ($p = 0.028$).

Forty-one patients (12%) reported depression, which was significantly associated with a KPS < 90 ($p = 0.0017$) and a Charlson Comorbidity Index ≥ 3 ($p = 0.0013$) (Table IV). Trends for associations with depression were found for previous or concurrent breast cancer/DCIS ($p = 0.023$), volume of radiation treatment including locoregional lymph nodes ($p = 0.015$) and nodal stage N1-3 ($p = 0.033$).

Nervousness was stated by 98 patients (29%). No investigated factor was significantly associated with nervousness, but trends for such an association were found for previous or concurrent breast cancer/DCIS ($p = 0.022$), upfront mastectomy ($p = 0.035$) and triple-negativity ($p = 0.042$) (Table V).

Loss of interest in usual activities was reported by 50 patients (15%) and showed a significant association with a KPS < 90 ($p < 0.0001$) (Table VI). Trends were observed for a Charlson Comorbidity Index ≥ 3 ($p = 0.011$), family history of breast cancer/DCIS ($p = 0.029$), invasive breast cancer ($p = 0.041$), preceding chemotherapy ($p = 0.022$) and volume of radiation treatment including locoregional lymph nodes ($p = 0.021$).

Discussion

Most patients with primary non-metastatic breast cancer receive breast-conserving surgery followed by radiotherapy (6). Moreover, selected patients with risk factors for developing a local or locoregional recurrence require

Table I. Associations of the investigated characteristics and worry (338 patients).

Characteristic		Worry, n (%)		p-Value
		No	Yes	
COVID-19 pandemic	Before	102 (63)	61 (37)	0.96
	During	109 (62)	66 (38)	
Age	≤60 Years	85 (50)	84 (50)	<0.0001
	≥61 Years	126 (75)	43 (25)	
Karnofsky performance score	90-100	172 (63)	103 (37)	0.92
	<90	39 (62)	24 (38)	
Charlson comorbidity index	2	137 (63)	80 (37)	0.72
	≥3	74 (61)	47 (39)	
Additional breast cancer/DCIS	No	194 (62)	117 (38)	0.95
	Yes	17 (63)	10 (37)	
History of additional tumor	No	187 (62)	115 (38)	0.58
	Yes	24 (67)	12 (33)	
Family history of malignancy	No	75 (68)	36 (32)	0.17
	Yes	136 (60)	91 (40)	
Family history of breast cancer/DCIS	No	134 (64)	76 (36)	0.50
	Yes	77 (60)	51 (40)	
Previous radiotherapy	No	192 (62)	120 (38)	0.24
	Yes	19 (73)	7 (27)	
Tumor type	DCIS	23 (70)	10 (30)	0.36
	Invasive cancer	188 (62)	117 (38)	
Type of surgery	BCS	189 (63)	113 (37)	0.86
	Mastectomy	22 (61)	14 (39)	
Chemotherapy pre-RT	No	138 (65)	74 (35)	0.19
	Yes	73 (58)	53 (42)	
Hormonal therapy pre-RT	No	165 (63)	95 (37)	0.47
	Yes	46 (59)	32 (41)	
Treatment volume of RT	Without LN	176 (65)	95 (35)	0.055
	With LN	35 (52)	32 (48)	
Primary tumor stage*	T1-2	173 (63)	103 (37)	0.25
	T3-4	15 (52)	14 (48)	
Nodal stage*	N0-1 _{mi}	141 (64)	80 (36)	0.21
	N1-3	47 (56)	37 (44)	
Distant metastasis*	No	187 (62)	115 (38)	0.56
	Yes	1 (33)	2 (67)	
Histologic grading*	G1-2	135 (63)	78 (37)	0.34
	G3	53 (58)	39 (42)	
Triple negative tumor*	No	177 (63)	103 (37)	0.058
	Yes	11 (44)	14 (56)	

BCS: Breast-conserving surgery; DCIS: ductal carcinoma *in situ*; LN: lymph nodes; RT: radiotherapy. *Invasive cancer only (n=305). When applying Bonferroni correction, p-values <0.0026 are significant and shown in bold.

radiation treatment after skin-sparing or radical mastectomy (6). In addition to diagnosis of breast cancer, just the being scheduled for post-operative irradiation can lead to significant emotional distress. In the study of Mose *et al*. that included 111 women irradiated with 56 Gy following BCS, 53% of the patients experienced distress due to the diagnosis of breast cancer and 48% of the patients felt distressed because of the imminent radiation treatment (10). Moreover,

Table II. Associations of the investigated characteristics and fears (338 patients).

Characteristic		Fear, n (%)		p-Value
		No	Yes	
COVID-19 pandemic	Before	87 (53)	76 (47)	0.71
	During	97 (55)	78 (45)	
Age	≤60 Years	74 (44)	95 (56)	<0.0001
	≥61 Years	110 (65)	59 (35)	
Karnofsky performance score	90-100	152 (55)	123 (45)	0.52
	<90	32 (51)	31 (49)	
Charlson comorbidity index	2	124 (57)	93 (43)	0.18
	≥3	60 (50)	61 (50)	
Additional breast cancer/DCIS	No	172 (55)	139 (45)	0.28
	Yes	12 (44)	15 (56)	
History of additional tumor	No	163 (54)	139 (46)	0.62
	Yes	21 (58)	15 (42)	
Family history of malignancy	No	65 (59)	46 (41)	0.29
	Yes	119 (52)	108 (48)	
Family history of breast cancer/DCIS	No	120 (57)	90 (43)	0.20
	Yes	64 (50)	64 (50)	
Previous radiotherapy	No	168 (54)	144 (46)	0.45
	Yes	16 (62)	10 (38)	
Tumor type	DCIS	18 (55)	15 (45)	0.99
	Invasive cancer	166 (54)	139 (46)	
Type of surgery	BCS	166 (55)	136 (45)	0.57
	Mastectomy	18 (50)	18 (50)	
Chemotherapy pre-RT	No	117 (55)	95 (45)	0.72
	Yes	67 (53)	59 (47)	
Hormonal therapy pre-RT	No	143 (55)	117 (45)	0.70
	Yes	41 (53)	37 (47)	
Treatment volume of RT	Without LN	154 (57)	117 (43)	0.076
	With LN	30 (45)	37 (55)	
Primary tumor stage*	T1-2	151 (55)	125 (45)	0.76
	T3-4	15 (52)	14 (48)	
Nodal stage*	N0-1 _{mi}	126 (57)	95 (43)	0.14
	N1-3	40 (48)	44 (52)	
Distant metastasis*	No	165 (55)	137 (45)	0.59
	Yes	1 (33)	2 (67)	
Histologic grading*	G1-2	118 (55)	95 (45)	0.60
	G3	48 (52)	44 (48)	
Triple negative tumor*	No	153 (55)	127 (45)	0.80
	Yes	13 (52)	12 (48)	

BCS: Breast-conserving surgery; DCIS: ductal carcinoma *in situ*; LN: lymph nodes; RT: radiotherapy. *Invasive cancer only (n=305). When applying Bonferroni correction, p-values <0.0026 are significant and shown in bold.

better pre-treatment emotional functioning was reported to be associated with improved overall quality of life at the end of treatment in a series of 75 postmenopausal women receiving adjuvant radiotherapy for breast cancer (9). Therefore, it is important to identify patients who will experience emotional distress prior to the radiotherapy course to provide psychological support timely before starting treatment. Compared to the previous study of Sohl

Table III. Associations of the investigated characteristics and sadness (338 patients).

Characteristic		Sadness, n (%)		p-Value
		No	Yes	
COVID-19 pandemic	Before	113 (69)	50 (31)	0.44
	During	128 (73)	47 (27)	
Age	≤60 Years	107 (63)	62 (37)	0.0012
	≥61 Years	134 (79)	35 (21)	
Karnofsky performance score	90-100	206 (75)	69 (25)	0.0022
	<90	35 (56)	28 (44)	
Charlson comorbidity index	2	163 (75)	54 (25)	0.038
	≥3	78 (64)	43 (36)	
Additional breast cancer/DCIS	No	228 (73)	83 (27)	0.0056
	Yes	13 (48)	14 (52)	
History of additional tumor	No	216 (72)	86 (28)	0.79
	Yes	25 (69)	11 (31)	
Family history of malignancy	No	84 (76)	27 (24)	0.21
	Yes	157 (69)	70 (31)	
Family history of breast cancer/DCIS	No	150 (71)	60 (29)	0.95
	Yes	91 (71)	37 (29)	
Previous radiotherapy	No	224 (72)	88 (28)	0.49
	Yes	17 (65)	9 (35)	
Tumor type	DCIS	26 (79)	7 (21)	0.32
	Invasive cancer	215 (70)	90 (30)	
Type of surgery	BCS	218 (72)	84 (28)	0.30
	Mastectomy	23 (44)	13 (36)	
Chemotherapy pre-RT	No	160 (75)	52 (25)	0.028
	Yes	81 (64)	45 (36)	
Hormonal therapy pre-RT	No	188 (72)	72 (28)	0.46
	Yes	53 (68)	25 (32)	
Treatment volume of RT	Without LN	199 (73)	72 (27)	0.082
	With LN	42 (63)	25 (37)	
Primary tumor stage*	T1-2	195 (71)	81 (29)	0.85
	T3-4	20 (69)	9 (31)	
Nodal stage*	N0-1 _{mi}	161 (73)	60 (27)	0.14
	N1-3	54 (64)	30 (36)	
Distant metastasis*	No	213 (71)	89 (29)	>0.99
	Yes	2 (67)	1 (33)	
Histologic grading*	G1-2	156 (73)	57 (27)	0.11
	G3	59 (64)	33 (36)	
Triple negative tumor*	No	196 (70)	84 (30)	0.53
	Yes	19 (76)	6 (24)	

BCS: Breast-conserving surgery; DCIS: ductal carcinoma *in situ*; LN: lymph nodes; RT: radiotherapy. *Invasive cancer only (n=305). When applying Bonferroni correction, p-values <0.0026 are significant and shown in bold.

et al., we investigated additional potential risk factors for emotional distress prior to radiotherapy for primary breast cancer. Our study focused on the six emotional problems considered in the National Comprehensive Cancer Network Distress Thermometer, *i.e.* worry, fears, sadness, depression, nervousness, and loss of interest in usual activities (11).

According to the results of this study, younger age was significantly associated with worry, fears and sadness. Lower

Table IV. Associations of the investigated characteristics and depression (337 patients).

Characteristic		Depression, n (%)		p-Value
		No	Yes	
COVID-19 pandemic	Before	142 (87)	21 (13)	0.70
	During	154 (89)	20 (11)	
Age	≤60 Years	143 (85)	25 (15)	0.13
	≥61 Years	153 (91)	16 (9)	
Karnofsky performance score	90-100	248 (91)	26 (9)	0.0017
	<90	48 (76)	15 (24)	
Charlson comorbidity index	2	199 (92)	17 (8)	0.0013
	≥3	97 (80)	24 (20)	
Additional breast cancer/DCIS	No	276 (89)	34 (11)	0.023
	Yes	20 (74)	7 (26)	
History of additional tumor	No	264 (88)	37 (12)	>0.99
	Yes	32 (89)	4 (11)	
Family history of malignancy	No	99 (90)	11 (10)	0.40
	Yes	197 (87)	30 (13)	
Family history of breast cancer/DCIS	No	178 (85)	31 (15)	0.056
	Yes	118 (92)	10 (8)	
Previous radiotherapy	No	274 (88)	37 (12)	0.54
	Yes	22 (85)	4 (15)	
Tumor type	DCIS	30 (91)	3 (9)	0.78
	Invasive cancer	266 (88)	38 (13)	
Type of surgery	BCS	264 (88)	37 (12)	>0.99
	Mastectomy	32 (89)	4 (11)	
Chemotherapy pre-RT	No	190 (90)	21 (10)	0.11
	Yes	106 (84)	20 (16)	
Hormonal therapy pre-RT	No	231 (89)	28 (11)	0.17
	Yes	65 (83)	13 (17)	
Treatment volume of RT	Without LN	243 (90)	27(10)	0.015
	With LN	53 (79)	14 (21)	
Primary tumor stage*	T1-2	239 (87)	36 (13)	0.55
	T3-4	27 (93)	2 (7)	
Nodal stage*	N0-1 _{mi}	198 (90)	22 (10)	0.033
	N1-3	68 (81)	16 (19)	
Distant metastasis*	No	264 (88)	37 (12)	0.33
	Yes	2 (67)	1 (33)	
Histologic grading*	G1-2	189 (89)	23 (11)	0.19
	G3	77 (84)	15 (16)	
Triple negative tumor*	No	243 (87)	36 (13)	0.75
	Yes	23 (92)	2 (8)	

BCS: Breast-conserving surgery; DCIS: ductal carcinoma *in situ*; LN: lymph nodes; RT: radiotherapy. *Invasive cancer only (n=304). When applying Bonferroni correction, p-values <0.0026 are significant and shown in bold.

(worse) performance score showed significant associations with sadness, depression, and loss of interest in usual activities. Higher comorbidity index was significantly associated with depression and showed trends for associations with sadness and loss of interest in usual activities. Previous or concurrent breast cancer/DCIS was almost significantly associated with sadness, and trends were found for associations with depression and nervousness.

Table V. Associations of the investigated characteristics and nervousness (338 patients).

Characteristic		Nervousness, n (%)		p-Value
		No	Yes	
COVID-19 pandemic	Before	115 (71)	48 (29)	0.86
	During	125 (71)	50 (29)	
Age	≤60 Years	121 (72)	48 (28)	0.81
	≥61 Years	119 (70)	50 (30)	
Karnofsky performance score	90-100	200 (73)	75 (27)	0.15
	<90	40 (63)	23 (37)	
Charlson comorbidity index	2	154 (71)	63 (29)	0.98
	≥3	86 (71)	35 (29)	
Additional breast cancer/DCIS	No	226 (73)	85 (27)	0.022
	Yes	14 (52)	13 (48)	
History of additional tumor	No	214 (71)	88 (29)	0.86
	Yes	26 (72)	10 (28)	
Family history of malignancy	No	79 (71)	32 (29)	0.96
	Yes	161 (71)	66 (29)	
Family history of breast cancer/DCIS	No	147 (70)	63 (30)	0.60
	Yes	93 (73)	35 (27)	
Previous radiotherapy	No	225 (72)	87 (28)	0.12
	Yes	15 (58)	11 (42)	
Tumor type	DCIS	26 (79)	7 (21)	0.30
	Invasive cancer	214 (70)	91 (30)	
Type of surgery	BCS	209 (69)	93 (31)	0.035
	Mastectomy	31 (86)	5 (14)	
Chemotherapy pre-RT	No	148 (70)	64 (30)	0.53
	Yes	92 (73)	34 (27)	
Hormonal therapy pre-RT	No	186 (72)	74 (28)	0.69
	Yes	54 (69)	24 (31)	
Treatment volume of RT	Without LN	191 (70)	80 (30)	0.67
	With LN	49 (73)	18 (27)	
Primary tumor stage*	T1-2	189 (68)	87 (32)	0.055
	T3-4	25 (86)	4 (14)	
Nodal stage*	N0-1 _{mi}	154 (70)	67 (30)	0.77
	N1-3	60 (71)	24 (29)	
Distant metastasis*	No	212 (70)	90 (30)	>0.99
	Yes	2 (67)	1 (33)	
Histologic grading*	G1-2	148 (69)	65 (31)	0.69
	G3	66 (72)	26 (28)	
Triple negative tumor*	No	192 (69)	88 (31)	0.042
	Yes	22 (88)	3 (12)	

BCS: Breast-conserving surgery; DCIS: ductal carcinoma *in situ*; LN: lymph nodes; RT: radiotherapy. *Invasive cancer only (n=305).

Moreover, trends were observed for associations of preceding chemotherapy with sadness and loss of interest in usual activities, and of treatment volumes of radiotherapy including lymph nodes with depression and loss of interest in usual activities. Additional trends were found for associations between nodal stage 1-3 and depression, between, mastectomy and nervousness, between triple-negativity and nervousness, between family history of breast cancer/DCIS and loss of interest in usual activities, and

Table VI. Associations of the investigated characteristics and loss of interest in usual activities (336 patients).

Characteristic		Loss of interest in usual activities, n (%)		
		No	Yes	p-Value
COVID-19 pandemic	Before	137 (84)	26 (16)	0.59
	During	149 (86)	24 (14)	
Age	≤60 Years	140 (84)	27 (16)	0.51
	≥61 Years	146 (86)	23 (14)	
Karnofsky performance score	90-100	243 (89)	30 (11)	<0.0001
	<90	43 (68)	20 (32)	
Charlson comorbidity index	2	191 (89)	24 (11)	0.011
	≥3	95 (79)	26 (21)	
Additional breast cancer/DCIS	No	265 (86)	44 (14)	0.26
	Yes	21 (78)	6 (22)	
History of additional tumor	No	257 (86)	43 (14)	0.42
	Yes	29 (81)	7 (19)	
Family history of malignancy	No	96 (87)	14 (13)	0.44
	Yes	190 (84)	36 (16)	
Family history of breast cancer/DCIS	No	171 (82)	38 (18)	0.029
	Yes	115 (91)	12 (9)	
Previous radiotherapy	No	265 (85)	45 (15)	0.52
	Yes	21 (81)	5 (19)	
Tumor type	DCIS	32 (97)	1 (3)	0.041
	Invasive cancer	254 (84)	49 (16)	
Type of surgery	BCS	257 (86)	43 (14)	0.42
	Mastectomy	29 (81)	7 (19)	
Chemotherapy pre-RT	No	186 (89)	24 (11)	0.022
	Yes	100 (79)	26 (21)	
Hormonal therapy pre-RT	No	221 (85)	38 (15)	0.84
	Yes	65 (84)	12 (16)	
Treatment volume of RT	Without LN	235 (87)	34 (13)	0.021
	With LN	51 (76)	16 (24)	
Primary tumor stage*	T1-2	230 (84)	44 (16)	0.87
	T3-4	24 (83)	5 (17)	
Nodal stage*	N0-1 _{mi}	188 (86)	31 (14)	0.12
	N1-3	66 (79)	18 (21)	
Distant metastasis*	No	252 (84)	48 (16)	0.41
	Yes	2 (67)	1 (33)	
Histologic grading*	G1-2	178 (84)	33 (16)	0.70
	G3	76 (83)	16 (17)	
Triple negative tumor*	No	233 (84)	45 (16)	>0.99
	Yes	21 (84)	4 (16)	

BCS: Breast-conserving surgery; DCIS: ductal carcinoma *in situ*; LN: lymph nodes; RT: radiotherapy. *Invasive cancer only (n=303). When applying Bonferroni correction, p-values <0.0026 are significant and shown in bold.

between invasive cancer and loss of interest in usual activities. During the interpretation of these results, the retrospective study design should be kept in mind. Retrospective studies always bear the risk of hidden selection biases. However, since a major goal of this study is the comparison between patients who presented before and patients who presented during the COVID-19 pandemic, the

study can currently not be performed as a prospective trial.

In previous studies investigating pre-radiotherapy emotional distress, younger age, cancer stage and mastectomy were identified as risk factors (2, 10). Mose *et al.* observed high distress levels in women being 58 years or younger (10), and Sohl *et al.* found significant associations between emotional upset and cancer stage or mastectomy (2). Some other predictors of emotional distress identified in our study were previously reported in different settings. In several studies, younger age was identified as predictor of distress. In 2011, Luutonen *et al.* presented the results of 276 patients who completed a questionnaire regarding distress, depression and unmet needs during a course of adjuvant radiotherapy for breast cancer (13). Age <53 years was an independent predictor of distress ($p=0.001$). In a cohort of 343 women with newly diagnosed breast cancer who completed the distress thermometer younger women (<50 years) experienced higher distress levels (14). In 2016, the results of a prospective observational study from The Netherlands were presented (15). This study included patients with breast cancer regardless of the type of treatment and evaluated clinical distress at 6 and 15 months after first diagnosis of cancer. On univariate analysis, younger age predicted enduring clinical distress (odds ratio=0.96). Moreover, in a systematic review of 42 studies, younger age was confirmed as predictor of distress in female breast cancer survivors (16). In a population-based cohort study following 16,495 women with newly diagnosed breast cancer, younger age was associated with distress during both the phase of hospital-based treatment and transitional survivorship (17).

The prognostic role of the performance status was also previously reported. In the prospective study from The Netherlands, lack of muscle strength, which generally means an impairment of the performance status, was a significant (odds ratio=1.82) predictor of enduring clinical distress (15). In the systematic review of Syrowatka *et al.* about female breast cancer survivors, lower physical activity, lower quality of physical health, and limitations in physical functioning were associated with distress (16). Moreover, in a survey-based study of 125 female patients with any stage of breast cancer recruited within five years of diagnosis, physical symptom burden was associated with depression, anxiety and distress (18). Associations between co-morbidity and distress were also previously described. In the prospective study from the Netherlands, having two or more co-morbidities was a significant (odds ratio=1.51) predictor of enduring clinical distress (15). In the systematic review of 42 studies, co-morbidities were associated with an increased risk of distress (16). So was rheumatologic disease in the population-based cohort study of Syrowatka *et al.* (17).

Chemotherapy was identified as predictor of distress in several reports including the Dutch prospective study

(OR=2.47) and the systematic review of 42 studies (15, 16, 19). More recently, results of a prospective study of 50 women with breast cancer were presented, in whom a significant increase in fatigue ($p<0.001$) and psychological distress ($p<0.001$) was observed when comparing post-chemotherapy results to baseline (prior to chemotherapy) (20). Moreover, the fact that mastectomy (compared to BCS) was associated with increased distress was reported in a prospective study from The Netherlands (OR=1.72) and in the systematic review of Syrowatka *et al.* (15, 16, 19). In addition, patients with any type of cancer who received or were scheduled for surgery experienced significantly more emotional distress than other patients in the study of Thomas *et al.* (21).

Furthermore, negative hormone receptor status, which is similar to triple-negativity in the present study, was a risk factor of distress in the study of Luutonen *et al.* (13). And more advanced cancer stage at the time of the first diagnosis was identified as predictor of distress in the systematic review of Syrowatka *et al.* (15). A more advanced nodal stage requires additional radiotherapy of locoregional lymph nodes, which showed a trend for more emotional distress in the present study. Moreover, irradiation of the locoregional lymph nodes is associated with a risk of additional late sequelae including lymphedema and brachial plexopathy, which likely contributes to higher levels of emotional distress. Invasive cancer also showed a trend toward more emotional distress in this study when compared to DCIS alone. This can be explained by the less favorable prognoses of invasive cancers. Moreover, trends were found for experiencing emotional distress in case of a positive own or family history of breast cancer/DCIS. These findings are supported by previous studies showing that the fear of recurrent breast cancer, which likely applies also to fear of second (contralateral) breast cancer, is an important issue and can cause significant distress and have a negative impact on quality of life (22-24). Moreover, being reminded of a relative's breast cancer disease will likely contribute to emotional distress.

In conclusion, the present study contributes to identification of patients scheduled for radiotherapy of primary breast cancer who have a high risk of emotional distress. This applies particularly to younger patients, patients with a poorer performance status, and patients with a higher comorbidity index. In addition, patients who received a mastectomy or preceding chemotherapy, patients with more advanced or aggressive tumors, and patients with own or family history of breast cancer/DCIS have an increased risk of emotional distress. All of these patients should receive psychological support as soon as possible and optimally before the start of their radiotherapy course. In contrast to the identified risk factors, the COVID-19 pandemic was not associated with an increased prevalence of emotional problems.

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., T.W.K., S.E.S. and T.B. participated in the design of the study. D.R., C.A.N. and L.D. provided the data, which were analyzed by D.R. The article drafted by D.R., S.E.S. and T.B. was reviewed and finally approved by all Authors.

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References

- Siegel RL, Miller KD, Fuchs HE and Jemal A: Cancer statistics, 2021. *CA Cancer J Clin* 71(1): 7-33, 2021. PMID: 33433946. DOI: 10.3322/caac.21654
- Sohl SJ, Schnur JB, Sucala M, David D, Winkel G and Montgomery GH: Distress and emotional well-being in breast cancer patients prior to radiotherapy: an expectancy-based model. *Psychol Health* 27(3): 347-361, 2012. PMID: 21678183. DOI: 10.1080/08870446.2011.569714
- Park JH, Chun M, Jung YS and Bae SH: Predictors of psychological distress trajectories in the first year after a breast cancer diagnosis. *Asian Nurs Res (Korean Soc Nurs Sci)* 11(4): 268-275, 2017. PMID: 29290274. DOI: 10.1016/j.anr.2017.10.003
- Danckert B, Ferlay J, Engholm G, Hansen HL, Johannesen TB, Khan S, Køtlum JE, Ólafsdóttir E, Schmidt LKH, Virtanen A and Storm HH: NORDCAN: Cancer incidence, mortality, prevalence and survival in the Nordic Countries, version 8.2. (26.03.2019). Association of the Nordic Cancer Registries. Danish Cancer Society, 2019. Available at: <https://www.ncr.nu> [Last accessed on May 24, 2021]
- Katalinic A, Pritzkeleit R and Waldmann A: Recent trends in breast cancer incidence and mortality in Germany. *Breast Care (Basel)* 4(2): 75-80, 2009. PMID: 20847883. DOI: 10.1159/000211526
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms, Version 4.3, 2020. Available at: <https://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/> [Last accessed on June 17, 2021]
- Duan Y, Wang L, Sun Q, Liu X, Ding S, Cheng Q, Xie J and Cheng ASK: Prevalence and determinants of psychological distress in adolescent and young adult patients with cancer: a multicenter survey. *Asia Pac J Oncol Nurs* 8(3): 314-321, 2021. PMID: 33850965. DOI: 10.4103/2347-5625.311005
- Herschbach P, Keller M, Knight L, Brandt T, Huber B, Henrich G and Marten-Mittag B: Psychological problems of cancer patients: a cancer distress screening with a cancer-specific questionnaire. *Br J Cancer* 91(3): 504-511, 2004. PMID: 15238979. DOI: 10.1038/sj.bjc.6601986
- Browall M, Ahlberg K, Karlsson P, Danielson E, Persson LO and Gaston-Johansson F: Health-related quality of life during adjuvant treatment for breast cancer among postmenopausal women. *Eur J Oncol Nurs* 12(3): 180-189, 2008. PMID: 18343197. DOI: 10.1016/j.ejon.2008.01.005
- Mose S, Budischewski KM, Rahn AN, Zander-Heinz AC, Bormeth S and Böttcher HD: Influence of irradiation on therapy-associated psychological distress in breast carcinoma patients. *Int J Radiat Oncol Biol Phys* 51(5): 1328-1335, 2001. PMID: 11728694. DOI: 10.1016/s0360-3016(01)01711-4
- Holland JC, Andersen B, Breitbart WS, Buchmann LO, Compas B, Deshields TL, Dudley MM, Fleishman S, Fulcher CD, Greenberg DB, Greiner CB, Handzo GF, Hoofring L, Hoover C, Jacobsen PB, Kvale E, Levy MH, Loscalzo MJ, McAllister-Black R, Mechanic KY, Palesh O, Pazar JP, Riba MB, Roper K, Valentine AD, Wagner LI, Zevon MA, McMillian NR and Freedman-Cass DA: Distress management. *J Natl Compr Canc Netw* 11(2): 190-209, 2013. PMID: 23411386. DOI: 10.6004/jnccn.2013.0027
- Rades D, Narvaez CA, Schild SE, Tvilsted S and Kjaer TW: Sleep disorders before and during the COVID-19 pandemic in patients assigned to adjuvant radiotherapy for breast cancer. *In Vivo* 35: 2253-2260, 2021. DOI: 10.21873/invivo.12498
- Luutonen S, Vahlberg T, Eloranta S, Hyväri H and Salminen E: Breast cancer patients receiving postoperative radiotherapy: distress, depressive symptoms and unmet needs of psychosocial support. *Radiother Oncol* 100(2): 299-303, 2011. PMID: 21316782. DOI: 10.1016/j.radonc.2011.01.014
- Mertz BG, Bistrup PE, Johansen C, Dalton SO, Deltour I, Kehlet H and Kroman N: Psychological distress among women with newly diagnosed breast cancer. *Eur J Oncol Nurs* 16(4): 439-443, 2012. PMID: 22036771. DOI: 10.1016/j.ejon.2011.10.001
- Lo-Fo-Wong DN, de Haes HC, Aaronson NK, van Abbema DL, den Boer MD, van Hezewijk M, Immink M, Kaptein AA, Menke-Pluijmers MB, Reyners AK, Russell NS, Schriek M, Sijtsema S, van Tienhoven G and Sprangers MA: Predictors of enduring clinical distress in women with breast cancer. *Breast Cancer Res Treat* 158(3): 563-572, 2016. PMID: 27417105. DOI: 10.1007/s10549-016-3896-7
- Syrowatka A, Motulsky A, Kurteva S, Hanley JA, Dixon WG, Meguerditchian AN and Tamblyn R: Predictors of distress in female breast cancer survivors: a systematic review. *Breast Cancer Res Treat* 165(2): 229-245, 2017. PMID: 28553684. DOI: 10.1007/s10549-017-4290-9
- Syrowatka A, Hanley JA, Weir DL, Dixon WG, Meguerditchian AN and Tamblyn R: Ability to predict new-onset psychological distress using routinely collected health data: a population-based cohort study of women diagnosed with breast cancer. *J Natl Compr Canc Netw* 16(9): 1065-1073, 2018. PMID: 30181418. DOI: 10.6004/jnccn.2018.7038
- McFarland DC, Shaffer KM, Tiersten A and Holland J: Physical symptom burden and its association with distress, anxiety, and depression in breast cancer. *Psychosomatics* 59(5): 464-471, 2018. PMID: 29525522. DOI: 10.1016/j.psych.2018.01.005
- Lo-Fo-Wong DNN, de Haes HCJM, Aaronson NK, van Abbema DL, den Boer MD, van Hezewijk M, Immink M, Kaptein AA, Menke-Pluijmers MBE, Reyners AKL, Russell NS, Schriek M, Sijtsema S, van Tienhoven G, Verdam MGE and Sprangers MAG: Risk factors of unmet needs among women with breast cancer in the post-treatment phase. *Psychooncology* 29(3): 539-549, 2020. PMID: 31785043. DOI: 10.1002/pon.5299

- 20 Oh PJ and Cho JR: Changes in fatigue, psychological distress, and quality of life after chemotherapy in women with breast cancer: a prospective study. *Cancer Nurs* 43(1): E54-E60, 2020. PMID: 30601265. DOI: 10.1097/NCC.0000000000000689
- 21 Thomas BC, NandaMohan V, Nair MK and Pandey M: Gender, age and surgery as a treatment modality leads to higher distress in patients with cancer. *Support Care Cancer* 19(2): 239-250, 2010. PMID: 20174987. DOI: 10.1007/s00520-009-0810-4
- 22 Kenne Sarenmalm E, Ohlén J, Jonsson T and Gaston-Johansson F: Coping with recurrent breast cancer: predictors of distressing symptoms and health-related quality of life. *J Pain Symptom Manage* 34(1): 24-39, 2007. PMID: 17544244. DOI: 10.1016/j.jpainsymman.2006.10.017
- 23 Martínez Arroyo O, Andreu Vafillo Y, Martínez López P and Galdón Garrido MJ: Emotional distress and unmet supportive care needs in survivors of breast cancer beyond the end of primary treatment. *Support Care Cancer* 27(3): 1049-1057, 2019. PMID: 30094729. DOI: 10.1007/s00520-018-4394-8
- 24 Johns SA, Stutz PV, Talib TL, Cohee AA, Beck-Coon KA, Brown LF, Wilhelm LR, Monahan PO, LaPradd ML, Champion VL, Miller KD and Giesler RB: Acceptance and commitment therapy for breast cancer survivors with fear of cancer recurrence: A 3-arm pilot randomized controlled trial. *Cancer* 126(1): 211-218, 2020. PMID: 31539169. DOI: 10.1002/cncr.32518

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