

Emotional Distress Prior to Chemoradiation for Rectal or Anal Cancer

DIRK RADES¹, AHMED AL-SALOOL¹, NATHAN Y. YU² and TOBIAS BARTSCHT^{3,4}

¹Department of Radiation Oncology, University of Lübeck, Lübeck, Germany;

²Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ, U.S.A.;

³Department of Hematology, Oncology and Stem Cell Transplantation, MSH Medical School Hamburg, Schwerin Campus, Schwerin, Germany;

⁴Department of Hematology and Oncology, University of Lübeck, Lübeck, Germany

Abstract. *Background/Aim:* Anticipation of chemoradiation has been reported to cause psychosocial distress in patients with rectal cancer. This study provides additional data regarding prevalence and risk factors of emotional distress in patients who received chemoradiation for rectal or anal cancer. *Patients and Methods:* Sixty-four patients were analyzed for emotional distress utilizing 12 factors. When applying the Bonferroni correction, p -values <0.0042 were considered significant. *Results:* Worry, fears, sadness, depression, nervousness, and loss of interest in usual activities were reported by 31%, 47%, 33%, 11%, 47%, and 19% of patients, respectively. More physical problems were associated with fears ($p=0.0030$) and loss of interest ($p=0.0021$). Strong trends were observed for associations between female sex and sadness ($p=0.0098$) and between lower performance score and worry ($p=0.0068$) or fears ($p=0.0064$). *Conclusion:* A considerable proportion of patients reported emotional distress prior to chemoradiation for rectal or anal cancer. High-risk patients may benefit from early psycho-oncological support.

Concurrent chemoradiation is a standard of care for many patients with rectal or anal cancer (1-3). Often associated with

Correspondence to: Prof. Dirk Rades, MD, FASTRO, Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23562 Lübeck, Germany. Tel: +49 45150045401, Fax: +49 45150045404, e-mail: dirk.rades@uksh.de

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significant side effects, chemoradiation for rectal or anal cancer may cause significant emotional distress (4). In a previous study, the recommendation for neoadjuvant chemoradiation caused more pronounced psychosocial distress than other factors in patients with resectable rectal cancer (5). Despite this finding, there is a lack of data investigating the prevalence of emotional distress and corresponding risk factors in patients with rectal or anal cancer scheduled for chemoradiation. The present study was performed to generate additional data for this situation and identify patients who are predisposed to experience emotional distress.

Patients and Methods

Data from 64 patients initially scheduled for concurrent chemoradiation of rectal or anal cancer were retrospectively analyzed with respect to pre-treatment emotional distress. The study was approved by the responsible local Ethics Committee at the University of Lübeck (registration number 2022-412). Forty-five patients had locally advanced rectal cancer, and 19 patients had anal cancer.

Of the 45 rectal cancer patients, 4 patients received upfront resection due to pending obstruction. Three of these patients received 50.4 Gy and 1 patient 59.4 Gy of RT (5×1.8 Gy per week) in combination with oral capecitabine (825 mg/m² twice daily). Of the other 41 rectal cancer patients, 30 patients received neoadjuvant chemoradiation with 50.4 Gy plus capecitabine ($n=18$) or two courses of 1,000 mg/m² of 5-fluorouracil (5-FU) on days 1-5 ($n=12$), four patients 54.0 Gy plus capecitabine, and one patient with metastatic disease and previous chemotherapy 54.0 Gy plus encorafenib and cetuximab. One patient with a neuroendocrine tumor received 50.4 Gy plus carboplatin/etoposide. In two patients, chemoradiation with 5-FU was stopped after 41.4 Gy and 45.0 Gy, respectively, of planned 50.4 Gy due to acute toxicity, and three patients received hypo-fractionated radiotherapy without concurrent chemotherapy.

Of the 19 patients with anal cancer, 13 patients received definitive chemoradiation with 1.8 Gy per fraction and total doses of 54.0 to 61.2 Gy (median dose=59.4 Gy) combined with two concurrent courses of Mitomycin C (10 mg/m² on day) and 5-FU (1,000 mg/m²



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Table I. Associations of the investigated characteristics and worry.

Characteristic		Worry, n (%)		p-Value
		Yes	No	
COVID-19 pandemic	Before (n=28)	7 (25)	21 (75)	0.34
	During (n=36)	13 (36)	23 (64)	
Number of physical problems	0-3 (n=38)	8 (21)	30 (79)	0.033
	≥4 (n=26)	12 (46)	14 (54)	
Age	≤67 Years (n=34)	11 (32)	23 (68)	0.84
	≥68 Years (n=30)	9 (30)	21 (70)	
Sex	Female (n=28)	12 (43)	16 (57)	0.077
	Male (n=36)	8 (22)	28 (78)	
Karnofsky performance score	≤80 (n=23)	12 (52)	11 (48)	0.0068
	≥90 (n=41)	8 (20)	33 (80)	
Primary tumor type	Rectal cancer (n=45)	15 (33)	30 (67)	0.58
	Anal cancer (n=19)	5 (26)	14 (74)	
T-category	2-3 (n=56)	16 (29)	40 (71)	0.24
	4 (n=8)	4 (50)	4 (50)	
Nodal status	Negative (n=25)	5 (20)	20 (80)	0.12
	Positive (n=39)	15 (38)	24 (62)	
Distant metastasis	No (n=57)	18 (32)	39 (68)	>0.99
	Yes (n=7)	2 (29)	5 (71)	
Surgery prior to RT	No (n=55)	16 (29)	39 (71)	0.44
	Yes (n=9)	4 (44)	5 (56)	
Own history of another malignancy	No (n=49)	16 (33)	33 (67)	0.76
	Yes (n=15)	4 (27)	11 (73)	
Family history of malignancy	No (n=29)	11 (38)	18 (62)	0.29
	Yes (n=35)	9 (26)	26 (74)	

COVID-19: Coronavirus Disease 2019; RT: radiotherapy. After Bonferroni correction, p -values <0.0042 are significant.

on days 1-4). One patient received definitive treatment with 55.8 Gy plus concurrent Mitomycin C (without 5-FU), three patients adjuvant chemoradiation with 55.8 to 59.4 Gy plus concurrent Mitomycin C/5-FU, and one patient adjuvant treatment including 45.0 Gy of external-beam radiotherapy plus concurrent Mitomycin C/5-FU followed by a brachytherapy boost (2×4 Gy).

In the entire cohort, 12 factors were analyzed for associations with emotional distress (worry, fears, sadness, depression, nervousness, loss of interest in usual activities) obtained from the National Comprehensive Cancer Network (NCCN) distress thermometer completed by the patients during their first visit to the department of radiotherapy (6). These factors included time of the COVID-19 pandemic (before vs. during), number of physical problems according to the distress thermometer (0-3 vs. ≥4), age (≤67 vs. ≥68 years, median=68 years), sex (female vs. male) Karnofsky performance score (KPS ≤80 vs. ≥90), primary tumor type (rectal cancer vs. anal cancer), primary tumor category (T2-3 vs. T4), nodal status (negative vs. positive), distant metastasis (no vs. yes), upfront surgery (no vs. yes), history of another malignancy (no vs. yes), and family history of malignancy (no vs. yes).

For statistical analyses, the Chi-square test was mainly used. Only if the number of patients in at least one subgroup was less than 5, the analyses were performed with the Fisher's exact test. After application of the Bonferroni correction for multiple comparisons, p -values <0.0042 were considered significant representing alpha levels <0.05. In case of p <0.01, results were considered as a strong trend, and in case of p <0.05 as a trend.

Results

Emotional problems addressed by the distress thermometer, *i.e.*, worry, fears, sadness, depression, nervousness, and loss of interest in usual activities, were reported by 31%, 47%, 33%, 11%, 47%, and 19% of patients, respectively. Of the 12 investigated factors, ≥4 physical problems showed significant associations with fears ($p=0.0030$) and loss of interest in usual activities ($p=0.0021$) and a trend regarding worry ($p=0.033$). Moreover, female sex showed a strong trend for associations with sadness ($p=0.0098$) and trends regarding fear ($p=0.014$) and nervousness ($p=0.014$). In addition, strong trends were found for associations between KPS ≤80 and worry ($p=0.0068$) or fear ($p=0.0064$), and a trend between KPS ≤80 and loss of interest in usual activities ($p=0.021$). The results regarding associations between the 12 investigated factors and the six emotional problems are shown in Table I, Table II, Table III, Table IV, Table V, and Table VI.

Discussion

Chemoradiation for rectal or anal cancer is associated with significant toxicity and emotional burden for patients. In the study of Chomiccki *et al.* that investigated 106 patients

Table II. Associations of the investigated characteristics and fears.

Characteristic		Fears, n (%)		p-Value
		Yes	No	
COVID-19 pandemic	Before (n=28)	11 (39)	17 (61)	0.28
	During (n=36)	19 (53)	17 (47)	
Number of physical problems	0-3 (n=38)	12 (32)	26 (68)	0.0030
	≥4 (n=26)	18 (69)	8 (31)	
Age	≤67 Years (n=34)	17 (50)	17 (50)	0.59
	≥68 Years (n=30)	13 (43)	17 (57)	
Sex	Female (n=28)	18 (64)	10 (36)	0.014
	Male (n=36)	12 (33)	24 (67)	
Karnofsky performance score	≤80 (n=23)	16 (70)	7 (30)	0.0064
	≥90 (n=41)	14 (34)	27 (66)	
Primary tumor type	Rectal cancer (n=45)	20 (44)	25 (56)	0.55
	Anal cancer (n=19)	10 (53)	9 (47)	
T-category	2-3 (n=56)	26 (46)	30 (54)	>0.99
	4 (n=8)	4 (50)	4 (50)	
Nodal status	Negative (n=25)	12 (48)	13 (52)	0.89
	Positive (n=39)	18 (46)	21 (54)	
Distant metastasis	No (n=57)	27 (47)	30 (53)	>0.99
	Yes (n=7)	3 (43)	4 (57)	
Surgery prior to RT	No (n=55)	24 (44)	31 (56)	0.28
	Yes (n=9)	6 (67)	3 (33)	
Own history of another malignancy	No (n=49)	25 (51)	24 (49)	0.23
	Yes (n=15)	5 (33)	10 (67)	
Family history of malignancy	No (n=29)	13 (45)	16 (55)	0.77
	Yes (n=35)	17 (49)	18 (51)	

COVID-19: Coronavirus Disease 2019; RT: radiotherapy. After Bonferroni correction, *p*-values <0.0042 are significant and shown in bold.

Table III. Associations of the investigated characteristics and sadness.

Characteristic		Sadness, n (%)		p-Value
		Yes	No	
COVID-19 pandemic	Before (n=28)	9 (32)	19 (68)	0.92
	During (n=36)	12 (33)	24 (67)	
Number of physical problems	0-3 (n=38)	9 (24)	29 (76)	0.060
	≥4 (n=26)	12 (46)	14 (54)	
Age	≤67 Years (n=34)	13 (38)	21 (62)	0.33
	≥68 Years (n=30)	8 (27)	22 (73)	
Sex	Female (n=28)	14 (50)	14 (50)	0.0098
	Male (n=36)	7 (19)	29 (81)	
Karnofsky performance score	≤80 (n=23)	11 (48)	12 (52)	0.055
	≥90 (n=41)	10 (24)	31 (76)	
Primary tumor type	Rectal cancer (n=45)	13 (29)	32 (71)	0.30
	Anal cancer (n=19)	8 (42)	11 (58)	
T-category	2-3 (n=56)	17 (30)	39 (70)	0.42
	4 (n=8)	4 (50)	4 (50)	
Nodal status	Negative (n=25)	7 (28)	18 (72)	0.51
	Positive (n=39)	14 (36)	25 (64)	
Distant metastasis	No (n=57)	18 (32)	39 (68)	0.67
	Yes (n=7)	3 (43)	4 (57)	
Surgery prior to RT	No (n=55)	17 (31)	38 (69)	0.46
	Yes (n=9)	4 (44)	5 (56)	
Own history of another malignancy	No (n=49)	17 (35)	32 (65)	0.76
	Yes (n=15)	4 (27)	11 (73)	
Family history of malignancy	No (n=29)	8 (28)	21 (72)	0.42
	Yes (n=35)	13 (37)	22 (63)	

COVID-19: Coronavirus Disease 2019; RT: radiotherapy. After Bonferroni correction, *p*-values <0.0042 are significant.

Table IV. Associations of the investigated characteristics and depression.

Characteristic		Depression, n (%)		p-Value
		Yes	No	
COVID-19 pandemic	Before (n=28)	2 (7)	26 (93)	0.45
	During (n=36)	5 (14)	31 (86)	
Number of physical problems	0-3 (n=38)	2 (5)	36 (95)	0.11
	≥4 (n=26)	5 (19)	21 (81)	
Age	≤67 Years (n=34)	3 (9)	31 (91)	0.70
	≥68 Years (n=30)	4 (13)	26 (87)	
Sex	Female (n=28)	5 (18)	23 (82)	0.22
	Male (n=36)	2 (6)	34 (94)	
Karnofsky performance score	≤80 (n=23)	3 (13)	20 (87)	0.69
	≥90 (n=41)	4 (10)	37 (90)	
Primary tumor type	Rectal cancer (n=45)	4 (9)	41 (91)	0.41
	Anal cancer (n=19)	3 (16)	16 (84)	
T-category	2-3 (n=56)	6 (11)	50 (89)	>0.99
	4 (n=8)	1 (13)	7 (88)	
Nodal status	Negative (n=25)	4 (16)	21 (84)	0.42
	Positive (n=39)	3 (8)	36 (92)	
Distant metastasis	No (n=57)	5 (9)	52 (91)	0.17
	Yes (n=7)	2 (29)	5 (71)	
Surgery prior to RT	No (n=55)	6 (11)	49 (89)	>0.99
	Yes (n=9)	1 (11)	8 (89)	
Own history of another malignancy	No (n=49)	6 (12)	43 (88)	>0.99
	Yes (n=15)	1 (7)	14 (93)	
Family history of malignancy	No (n=29)	4 (14)	25 (86)	0.69
	Yes (n=35)	3 (9)	32 (91)	

COVID-19: Coronavirus Disease 2019; RT: radiotherapy. After Bonferroni correction, *p*-values <0.0042 are significant.

Table V. Associations of the investigated characteristics and nervousness.

Characteristic		Nervousness, n (%)		p-Value
		Yes	No	
COVID-19 pandemic	Before (n=28)	12 (43)	16 (57)	0.57
	During (n=36)	18 (50)	18 (50)	
Number of physical problems	0-3 (n=38)	14 (37)	24 (63)	0.052
	≥4 (n=26)	16 (62)	10 (38)	
Age	≤67 Years (n=34)	16 (47)	18 (53)	0.97
	≥68 Years (n=30)	14 (47)	16 (53)	
Sex	Female (n=28)	18 (64)	10 (36)	0.014
	Male (n=36)	12 (33)	24 (67)	
Karnofsky performance score	≤80 (n=23)	14 (61)	9 (39)	0.093
	≥90 (n=41)	16 (39)	25 (61)	
Primary tumor type	Rectal cancer (n=45)	23 (51)	22 (49)	0.30
	Anal cancer (n=19)	7 (37)	12 (63)	
T-category	2-3 (n=56)	25 (45)	31 (55)	0.34
	4 (n=8)	5 (63)	3 (38)	
Nodal status	Negative (n=25)	10 (40)	15 (60)	0.38
	Positive (n=39)	20 (51)	19 (49)	
Distant metastasis	No (n=57)	26 (46)	31 (54)	0.67
	Yes (n=7)	4 (57)	3 (43)	
Surgery prior to RT	No (n=55)	25 (45)	30 (55)	0.72
	Yes (n=9)	5 (56)	4 (44)	
Own history of another malignancy	No (n=49)	24 (49)	25 (51)	0.54
	Yes (n=15)	6 (40)	9 (60)	
Family history of malignancy	No (n=29)	11 (38)	18 (62)	0.19
	Yes (n=35)	19 (54)	16 (46)	

COVID-19: Coronavirus Disease 2019; RT: radiotherapy. After Bonferroni correction, *p*-values <0.0042 are significant.

Table VI. Associations of the investigated characteristics and loss of interest in usual activities.

Characteristic		Loss of interest in usual activities, n (%)		p-Value
		Yes	No	
COVID-19 pandemic	Before (n=28)	6 (21)	22 (79)	0.63
	During (n=36)	6 (17)	30 (83)	
Number of physical problems	0-3 (n=38)	2 (5)	36 (95)	0.0021
	≥4 (n=26)	10 (38)	16 (62)	
Age	≤67 Years (n=34)	6 (18)	28 (82)	0.81
	≥68 Years (n=30)	6 (20)	24 (80)	
Sex	Female (n=28)	7 (25)	21 (75)	0.26
	Male (n=36)	5 (14)	31 (86)	
Karnofsky performance score	≤80 (n=23)	8 (35)	15 (65)	0.021
	≥90 (n=41)	4 (10)	37 (90)	
Primary tumor type	Rectal cancer (n=45)	7 (16)	38 (84)	0.31
	Anal cancer (n=19)	5 (26)	14 (74)	
T-category	2-3 (n=56)	10 (18)	46 (82)	0.64
	4 (n=8)	2 (25)	6 (75)	
Nodal status	Negative (n=25)	5 (20)	20 (80)	0.84
	Positive (n=39)	7 (18)	32 (82)	
Distant metastasis	No (n=57)	10 (18)	47 (82)	0.61
	Yes (n=7)	2 (29)	5 (71)	
Surgery prior to RT	No (n=55)	9 (16)	46 (84)	0.35
	Yes (n=9)	3 (33)	6 (67)	
Own history of another malignancy	No (n=49)	9 (18)	40 (82)	>0.99
	Yes (n=15)	3 (20)	12 (80)	
Family history of malignancy	No (n=29)	6 (21)	23 (79)	0.72
	Yes (n=35)	6 (17)	29 (83)	

COVID-19: Coronavirus Disease 2019; RT: radiotherapy. After Bonferroni correction, *p*-values <0.0042 are significant and shown in bold.

receiving neoadjuvant chemoradiation for stage II or III upper rectal cancer, 42% of patients experienced acute toxicities and 24.5% of patients developed late toxicities (4). Moreover, early and late complications of surgery occurred in 27.4% and 9.4% of patients, respectively. The possibility of chemoradiation-related side effects may cause emotional distress. In our previous study of 42 patients with rectal or anal cancer, 42.9% of the patients reported sleep disorders prior to their course of chemoradiation (7). These disorders were triggered by several factors including emotional problems. In the present study, the frequencies of the six investigated emotional problems ranged between 11% and 47% (median 32%). In other studies that evaluated psychological distress including emotional problems following the treatment of rectal cancer, the prevalence ranged between 36% and 43% (8-10). The figures demonstrate that emotional distress is a relevant problem for these patients. Therefore, it is important to identify risk factors prior to the start of treatment. This would enable physicians to organize early psycho-oncological support for patients who are at risk of experiencing burdensome emotional distress.

In the present study, emotional distress was significantly associated with a greater number of physical problems. Moreover, strong trends for associations with emotional

problems were found for female sex and a lower Karnofsky performance score. Associations between physical problems and emotional distress have been previously described in other settings of patients with rectal or anal cancer. In the study of Benedict *et al.* including 70 patients treated for rectal or anal cancer, depression was positively correlated with worse diarrhea and other gastrointestinal symptoms, and anxiety with worse gastrointestinal symptoms (11). In another previous study, bowel dysfunction following resection of rectal cancer, particularly the fear of incontinence, had a negative impact on the patients' social functioning (12). In the study of Chambers *et al.*, having a permanent stoma and fatigue were risk factors for more pronounced psychological distress (13). Moreover, in our previous study, a greater number of physical problems was significantly ($p=0.0004$) associated with the occurrence of sleep disorders (7). Potential associations between female sex and emotional distress were also previously reported. In the study of Bencova *et al.* in patients with rectal cancer who were scheduled for neoadjuvant chemoradiation, psychosocial problems appeared more pronounced in female patients (5). In addition, patient-reported distress scores were significantly higher in women than in men (5.0 vs. 3.0, $p<0.001$) in another study of 238 patients with colorectal cancers not limited to a

specific treatment regimen (14). In our previous study, the prevalence of sleep disorders was non-significantly higher in female than in male patients (67% vs. 33%, $p=0.061$). In that study, the prevalence of sleep disorders was associated with a Karnofsky performance score of 60-80 vs. 90-100 (56% vs. 44%, $p=0.044$) (7). Moreover, in a study of patients with colorectal cancer being in remission for at least 24 months, the Karnofsky performance score was negatively correlated to the level of psychological distress (10). A weakness of this study is the retrospective nature. However, as the first study of its kind, it is hypothesis-generating and may help physicians identify high-risk patients who may benefit from early psycho-oncological support.

In conclusion, 47% of the patients in this study reported fear and nervousness and >30% of patients worry and sadness as indicators of emotional distress prior to chemoradiation for rectal or anal cancer. In patients with ≥ 4 physical problems, female sex, or reduced performance status, early psycho-oncological support may provide a benefit.

Conflicts of Interest

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

Authors' Contributions

All Authors participated in the study design. A. A.-S. and D.R. collected the data, which were analyzed by D.R. The article drafted by D.R. and N.Y.Y. was reviewed and finally approved by all Authors.

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