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Emotionaler Stress vor einer Strahlentherapie bei Patient*innen mit malignen Tumoren

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Abkürzungsverzeichnis

Abb.	Abbildung(en)
BT	Brachytherapie
EBRT	External Beam Radiotherapy (Perkutane Strahlentherapie)
HDR	High Dose Rate
IGRT	Image Guided Radiotherapy (Bildgesteuerte Strahlentherapie)
IORT	Intraoperative Radiotherapie
KPS	Karnofsky Performance Score (Karnofsky-Index)
LC	Lung Cancer (Lungenkarzinom)
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small Cell Lung Cancer (nicht-kleinzelliges Lungenkarzinom)
PSA	Prostataspezifisches Antigen
RT	Radiotherapie
SBRT	Stereotactic Body Radiation Therapy (Körperstereotaxie)
SCLC	Small Cell Lung Cancer (Kleinzelliges Lungenkarzinom)
VMAT	Volumetric Modulated Arc Therapy
WHO	World Health Organization (Weltgesundheitsorganisation)

I. Einleitung

Krebs verursacht seit über zwei Dekaden mehr als ein Viertel aller Todesfälle in Deutschland mit 231.000 Todesfällen im Jahr 2019 (117). Jedes Jahr erkranken annähernd 500.000 Männer und Frauen in Deutschland an Krebs (107). Ende 2017 lebten in Deutschland insgesamt 4.65 Mio. Personen mit bzw. nach einer Krebserkrankung, darunter 2.10 Mio. Männer und 2.55 Mio. Frauen (6). Erfreulicherweise haben sich durch den medizinischen Fortschritt die Überlebensraten bei vielen Krebserkrankungen über die Jahre deutlich verbessert (4,45). Mittlerweile überleben 50% der Männer und 58% der Frauen die ersten fünf Jahre nach einer Krebsdiagnose (107). Diese Statistik zeigt heutzutage, wie wirksam die aktuelle onkologische Therapie ist. Die zentralen Säulen der onkologischen Therapie bestehen aus Operation, Strahlentherapie und medikamentöser Tumortherapie (112). Viele Patient*innen mit einer malignen Erkrankung benötigen eine Strahlentherapie (7,9,13,27). Die Strahlentherapie wird indiziert, um eine Heilung bzw. Tumorkontrolle zu erreichen oder Beschwerden zu lindern (19). Sie kann als alleinige Behandlungsmethode, in Kombination mit Chemotherapie (Radiochemotherapie) und nach (adjuvant) oder vor (neoadjuvant) einer Operation eingesetzt werden (112). Einige Krebsarten, z.B. lokal begrenzter Kehlkopfkrebs oder Prostatakrebs, können durch eine alleinige Strahlentherapie geheilt werden (112). Es gibt verschieden Arten und Techniken der Strahlentherapie, die in der letzten Zeit weiterentwickelt wurden (112). Die technischen Weiterentwicklungen (Konformationsbestrahlung, Intensitätsmodulierte Strahlentherapie (IMRT), Stereotaktische Bestrahlung („Gamma Knife, CyberKnife, Strahlenchirurgie“), Bildgesteuerte Strahlentherapie (IGRT), Ionentherapie (Protonen-, Schwerionenbestrahlung), Intraoperative Radiotherapie (IORT)) ermöglichen es, die Strahlen in bestimmten Fällen noch genauer auf das gewünschte Zielgebiet zu lenken (29). Auf diese Weise kann das Tumorvolumen mit mehr Strahlendosis bestrahlt, die Nachbarorgane besser geschont und damit die Heilungschancen nochmals verbessert und die Nebenwirkungen geringer gehalten werden (29). Je nach Tumorentität, -stadium und -lage sowie Allgemeinzustand der Patient*innen kann empfohlen werden, welche Bestrahlungsmethode und -technik sowie Therapiekonzept für die Behandlung am besten geeignet ist (111).

Trotz des medizinischen Fortschritts hinsichtlich der Bestrahlungstechniken und -konzepte ist weiterhin mit Nebenwirkungen der Behandlung zu rechnen. Grundsätzlich unterscheidet man akute Nebenwirkungen, das heißt solche, die bereits während der Strahlentherapie auftreten, von Spätreaktionen, die Monate bis Jahre nach der Behandlung eintreten können (29). Beispiele für akute Nebenwirkungen sind Schleimhautentzündungen im Mund oder in

der Speiseröhre, wenn der Kopf-Hals-Bereich bestrahlt wird, Übelkeit oder Durchfälle bei Bestrahlung im Bauchbereich oder Hautrötungen bei Bestrahlung der Brust (29). Als Spätreaktionen können Hautverfärbungen oder Verhärtungen des Unterhautfettgewebes und selten Gewebenekrose auftreten (29).

Die Diagnose „Krebs“ löst bei den Betroffenen häufig große Ängste und Sorgen aus, was mit emotionalem Stress verbunden sein kann. Dies wird durch zahlreiche Studien belegt (10,16,18,36,41,82,83,89,124,128,131,133,136). Ängste, Sorgen und emotionaler Stress können bei den Patient*innen noch verstärkt werden, wenn die Betroffenen eine Strahlentherapie erhalten sollen. Dies liegt unter anderem daran, dass in der Bevölkerung über die Strahlentherapie sehr wenig bekannt ist (29). Selbst im Medizinstudium nimmt dieses Fach nur einen kleinen Raum ein, so dass sogar angehende Ärzt*innen oft nur wenig darüber wissen (29).

Neben dem Risiko für belastende Nebenwirkungen einer Strahlentherapie oder Radiochemotherapie sind hierfür häufig Bedenken hinsichtlich der Strahlenbelastung und der Abhängigkeit von „High Tech“-Geräten, für emotionalen Stress verantwortlich (3,15,18,21,26,33,34,39,43,44,51,55,78,79,81,90.98,99,102,103,104,106,119,125,126,129, 130,134,137).

Angaben zur Prävalenz von emotionalem Stress speziell vor einer Strahlentherapie sind in der Literatur kaum vorhanden. Gleiches gilt für mögliche Risikofaktoren. Somit sind weitere Studien in diesem Bereich erforderlich. Im Rahmen dieser Dissertation wurde bei Patient*innen mit verschiedenen malignen Erkrankungen die Prävalenz von allen Aspekten des emotionalen Stresses, die im NCCN Distress-Thermometer aufgeführt sind (Sorgen, Ängste, Traurigkeit, Depression, Nervosität, Verlust des Interesses an alltäglichen Aktivitäten) vor Beginn einer Strahlentherapie ermittelt und der Einfluss möglicher Risikofaktoren untersucht. Die Daten zur Ermittlung der Prävalenz der sechs Aspekte von Emotionalem Stress wurden mit Hilfe des Distress-Thermometers erhoben, das von den Patient*innen vor Beginn einer Strahlentherapie ausgefüllt wurde. Aus deren Akten wurden die weiteren Daten zur Untersuchung möglicher Risikofaktoren erhoben.

Da sich die Strahlentherapie bei den Tumorentitäten unter anderem hinsichtlich Dosis, Gesamtbehandlungszeit, Technik, Kombination mit Systemtherapien unterscheidet und dies auch auf Patientencharakteristika zutrifft, ist es sinnvoll, separate Studien für einzelne Tumorentitäten durchzuführen, um tumorspezifische Prävalenzen und Risikofaktoren für emotionalen Stress vor Beginn einer Strahlentherapie zu ermitteln.

Dies war zuvor bereits für Patientinnen, die aufgrund eines Mammakarzinoms bestrahlt wurden, erfolgt (96). In der vorliegenden Dissertation wurden jetzt Prävalenz und

Risikofaktoren für emotionalen Stress vor einer Bestrahlung bei weiteren Tumorentitäten untersucht, nämlich bei Gliomen, Kopf-Hals-Karzinomen, Lungenkarzinomen, Rektum-/Analkarzinomen, gynäkologischen Malignomen und Prostatakarzinomen. Die Kenntnis der Risikofaktoren wird zur Identifizierung von Patient*innen mit entsprechender maligner Erkrankung beitragen, die vor ihrer Strahlentherapie oder Radiochemotherapie zeitnah psychoonkologische Unterstützung benötigen können.

II. Prävalenz und Risikofaktoren für emotionalen Stress vor einer Strahlentherapie bei Patient*innen mit malignen Erkrankungen

II.1 Emotionaler Stress vor Radiochemotherapie oder alleiniger Strahlentherapie von Kopf-Hals-Karzinomen (Publikation 1)

Radiotherapie mit oder ohne begleitende Chemotherapie ist eine Standardbehandlung bei lokal fortgeschrittenen Kopf-Hals-Karzinomen und häufig mit erheblichen akuten und späten Toxizitäten verbunden, die zu emotionalem Stress führen können. Wir haben die Prävalenz und die Risikofaktoren von emotionalen Problemen bei Erkrankten mit Kopf-Hals-Karzinomen vor Beginn der Strahlentherapie ausgewertet.

Zwölf Eigenschaften wurden retrospektiv bei 213 Patient*innen für einen möglichen Zusammenhang mit emotionalen Problemen (Sorgen, Ängste, Traurigkeit, Depression, Nervosität und Verlust des Interesses an alltäglichen Aktivitäten) untersucht. Statistische Analysen wurden mit dem Chi-Quader-Test oder (wenn die Anzahl der Erkrankten in mindestens einer Untergruppe <5 war) dem exakten Test nach Fisher (Fisher's Exact Test) durchgeführt. Bei Anwendung der Bonferroni-Korrektur zur Adjustierung der Signifikanzniveaus der Einzeltests bei Durchführung multipler Tests entsprach ein p-Wert < 0,0042 einem Alpha-Fehler von < 5% und wurde daher als signifikant angesehen. Außerdem wurden p-Werte < 0,07 als Trend gewertet.

Mindestens ein emotionales Problem wurde von 131 Erkrankten (61,5%) angegeben. Die spezifische Prävalenz bei separater Betrachtung der sechs emotionalen Probleme bewegte sich zwischen 10% und 44% (Abb. I). Ein signifikanter Zusammenhang mit allen sechs emotionalen Problemen ergab sich für die höhere Anzahl körperlicher Beschwerden (p<0,0001). Ferner war Traurigkeit signifikant mit dem weiblichen Geschlecht assoziiert (p=0,0013). Trends für einen Zusammenhang wurden zwischen weiblichem Geschlecht und Ängsten (p=0,0097), einer weiteren Tumorerkrankung in der Anamnese und Traurigkeit (p=0,043), schlechterem Allgemeinzustand und Nervosität (p=0,012) sowie zwischen Tumorlokalisation (Oropharynx/Mundhöhle) und Nervosität (p=0.063) beobachtet (Tabelle I, Abb. II und III).

Emotionaler Stress vor einer Strahlentherapie von Kopf-Hals-Karzinomen ist häufig. Mehr als 60% der Erkrankten in dieser Studie gaben emotionalen Stress vor Beginn der Strahlentherapie an. Insbesondere Patient*innen mit Risikofaktoren für emotionalen Stress können von einer frühzeitigen psycho-onkologischen Unterstützung profitieren.

Abb. I. Prävalenz der sechs Aspekte von emotionalem Stress bei Patient*innen mit Kopf-Hals-Karzinomen

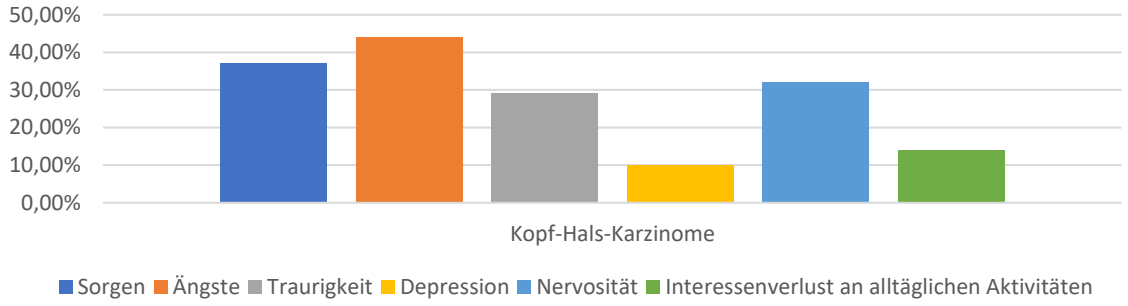


Tabelle I. Signifikante Assoziation bzw. Trends für Assoziationen zwischen Risikofaktoren und Aspekten von emotionalem Stress bei Patient*innen mit Kopf-Hals-Karzinomen vor Strahlentherapie

Aspekte von emotionalem Stress	Karnofsky-Index	Geschlecht	Anzahl physischer Probleme	Ja: n (%)	Nein: n (%)	p-Wert
Sorgen			≤4 (n=124) ≥5 (n=89)	25 (20) 54 (61)	99 (80) 35 (39)	**<0.0001**
Depression			≤4 (n=124) ≥5 (n=89)	2 (2) 19 (21)	122(98) 70 (79)	**<0.0001**
Traurigkeit			≤4 (n=124) ≥5 (n=89)	18 (15) 43 (48)	106(85) 46 (52)	**<0.0001**
Traurigkeit		weiblich (n=52) männlich (n=161)		24 (46) 37 (23)	28 (54) 124(77)	**0.0013**
Ängste		weiblich (n=52) männlich (n=161)		31 (60) 63 (39)	21 (40) 98 (61)	0.0097
Nervosität	≤80 (n=91) ≥90 (n=122)			38 (42) 31 (25)	53 (58) 91 (75)	0.012

Abb. II. Signifikante Assoziationen zwischen der Anzahl physischer Probleme und Sorgen, Traurigkeit sowie Depression bei Patient*innen mit Kopf-Hals-Karzinomen vor Strahlentherapie

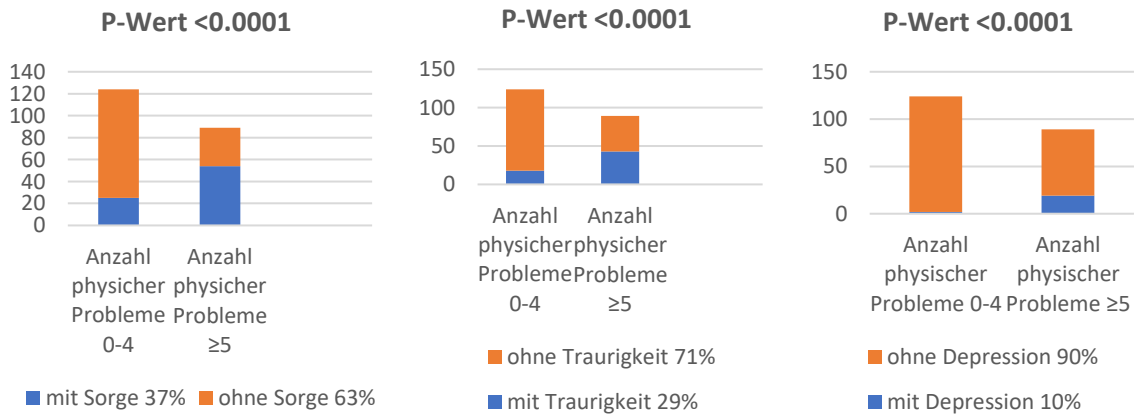
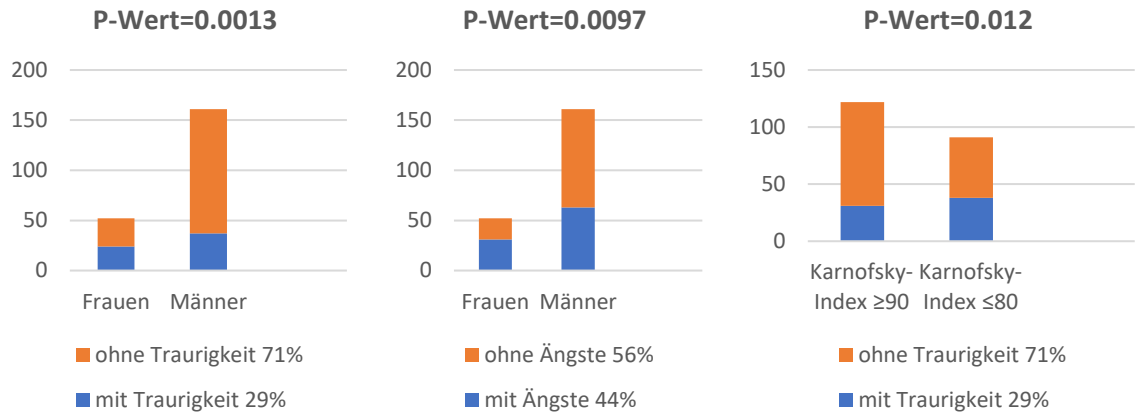


Abb. III. Signifikante Assoziation zwischen Geschlecht und Traurigkeit sowie Trends für Assoziationen zwischen Geschlecht und Ängsten sowie zwischen Karnofsky-Index und Traurigkeit bei Patient*innen mit Kopf-Hals-Karzinomen vor Strahlentherapie



II.2 Prävalenz und Risikofaktoren für emotionalen Stress vor einer Strahlentherapie bei Patient*innen mit einem Lungenkarzinom (Publikation 2)

Die Lebensqualität von Patient*innen mit Lungenkarzinom kann durch Stress beeinträchtigt werden. Diese Studie untersuchte die Prävalenz von emotionalem Stress und mögliche Risikofaktoren in einer Kohorte von Patient*innen mit einem Lungenkarzinom, bei denen eine Strahlentherapie oder eine Radiochemotherapie geplant war.

Bei 144 Patient*innen wurden 14 potentielle Risikofaktoren retrospektiv untersucht. Zu diesen Faktoren gehörten die Coronavirus-Erkrankung 2019 (vor vs. während der COVID-19-Pandemie), die Anzahl der körperlichen Probleme gemäß Distress-Thermometer (0-4 vs. ≥5 Probleme), Alter (≤69 vs. ≥70 Jahre, median=69 Jahre); Geschlecht (weiblich vs. männlich); Karnofsky-Performance-Score (≤80 vs. ≥90), Primärtumorkategorie (T1-T2 vs. T3-T4); Lymphknotenkategorie (N0–N1 vs. N2–N3), Fernmetastasierung (nein vs. ja), Histologie (NSCLC vs. SCLC), Operation vor Strahlentherapie (nein vs. ja); Radiochemotherapie (nein vs. ja), SBRT (nein vs. ja), weiterer Tumor in eigener Vorgeschichte (nein vs. ja) und Familienanamnese einer Tumorerkrankung (nein vs. ja). Emotionaler Stress wurde wiederum mit dem NCCN Distress-Thermometer bewertet. Die statistischen Analysen wurden mit dem Chi-Quadrat-Test und dem Fisher's Exact Test durchgeführt. Nach Anwendung der Bonferroni-Korrektur wurden p-Werte <0,0036 als signifikant betrachtet (Alpha-Fehler 5%). Außerdem wurden p-Werte <0,05 als Hinweis auf einen Trend angesehen.

Mindestens ein emotionales Problem (Sorgen, Ängste, Traurigkeit, Depression, Nervosität, Interessenverlust) wurde von der Mehrheit der Patient*innen (n=93, 65%) angegeben. Die Prävalenz dieser Probleme betrug 37 %, 38 %, 31 %, 15 %, 32 % bzw. 23 % (Abb. IV). Körperliche Probleme waren signifikant mit Sorgen (p=0,0029), Ängsten (p=0,0030),

Traurigkeit (p<0,0001), Depression (p=0,0008), Nervosität (p<0,0001) und Interessenverlust (p<0,0001) assoziiert. Ein Alter von ≤69 Jahren war mit Sorgen (p=0,0003) und weibliches Geschlecht mit Ängsten (p=0,0002) und Traurigkeit (p=0,0026) assoziiert. Es wurden Trends für Assoziationen von Alter mit Traurigkeit (p=0,045), weiblichem Geschlecht mit Nervosität (p=0,034) und Radiochemotherapie mit Sorgen (p=0,027) gefunden (Tabellen II und III, Abb. V und VI). Viele Patient*innen mit Lungenkarzinom, die eine Strahlentherapie erhalten sollen, leiden unter emotionalem Stress. Gerade für Risikopatient*innen kann eine frühzeitige psychoonkologische Hilfestellung wichtig sein.

Abb. IV. Die Prävalenz der sechs Aspekte von emotionalem Stress bei Patient*innen mit einem Lungenkarzinom

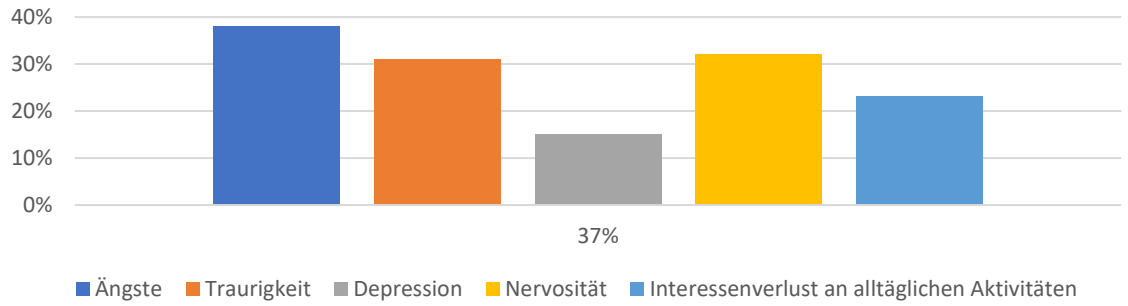


Tabelle II. Signifikante Assoziationen bzw. Trends für Assoziationen zwischen Risikofaktoren und Aspekten von emotionalem Stress bei Patient*innen mit Lungenkarzinom vor Strahlentherapie

Aspekte von emotionalem Stress	Alter	Geschlecht	Anzahl physischer Probleme	Ja: N (%)	Nein: N (%)	p-Wert
Traurigkeit			0-4 (n=75) ≥5 (n=69)	12 (16) 33 (48)	63 (84) 36 (52)	**<0.0001**
Ängste		weiblich (n=54) männlich (n=90)		31 (57) 24 (27)	23 (43) 66 (73)	**0.0002**
Sorgen	≤69 Jahre (n=75) ≥70 Jahre (n=69)			38 (51) 15 (22)	37 (49) 54 (78)	**0.0003**
Traurigkeit	≤69 Jahre (n=75) ≥70 Jahre (n=69			29 (39) 16 (23)	46 (61) 53 (77)	0.045
Nervosität		weiblich (n=54) männlich (n=90)		23 (43) 23 (26)	31 (57) 67 (74)	0.034

Tabelle III. Trend für eine Assoziation zwischen Radiochemotherapie und Sorgen bei Patient*innen mit Lungenkarzinom vor Strahlentherapie

Aspekt von emotionalem Stress	Radiochemotherapie	Ja: n (%)	Nein: n (%)	p-Wert
Sorgen	Nein (n=85) Ja (n=59)	25 (29) 28 (47)	60 (71) 31 (53)	0.027

Abb. V. Signifikante Assoziationen zwischen der Anzahl physischer Probleme und Traurigkeit, Geschlecht und Ängsten sowie zwischen Alter und Nervosität bei Patient*innen mit Lungenkarzinom vor Strahlentherapie

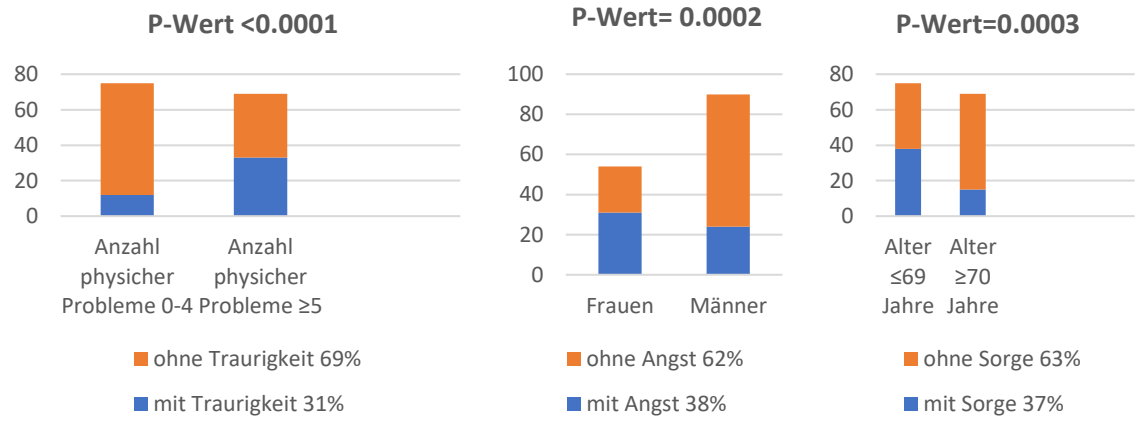
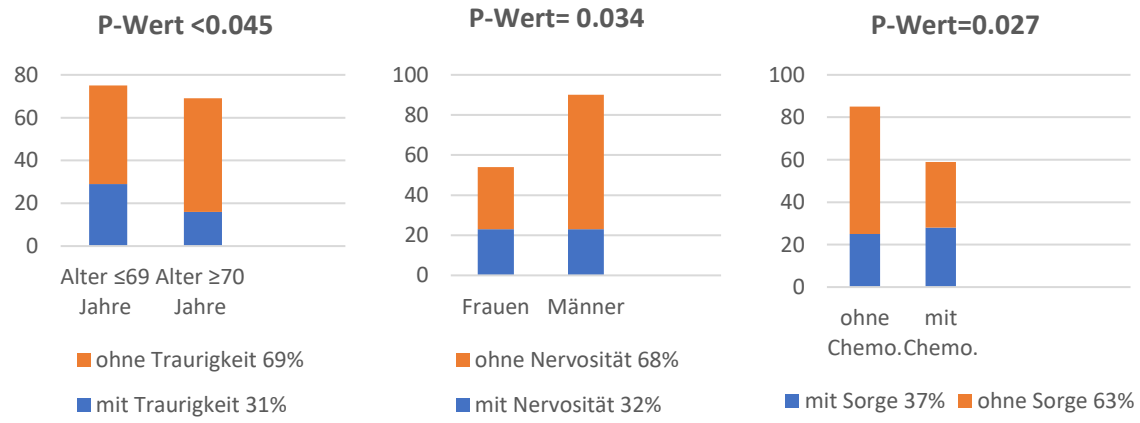


Diagramm VI. Trend für Assoziationen zwischen Alter und Traurigkeit, Geschlecht und Nervosität sowie zwischen Radiochemotherapie (Chemo.) und Sorge bei Patient*innen mit Lungenkarzinom vor Strahlentherapie



II.3 Prätherapeutischer emotionaler Stress bei Patientinnen, die eine Strahlentherapie bei gynäkologischen Malignomen erhalten haben (Publikation 3)

Auch Patientinnen mit gynäkologischen Malignomen, die für eine perkutane Strahlentherapie oder Brachytherapie ausgewählt wurden, können emotionalen Stress erfahren. Unser Ziel war es, Patientinnen zu identifizieren, die von einer frühen psychoonkologischen Intervention profitieren können.

Wir untersuchten 10 potenzielle Risikofaktoren für emotionalen Stress, wiederum unter Verwendung des NCCN Distress-Thermometers, in einer retrospektiven Serie von 122 Patientinnen, bei denen eine Strahlentherapie aufgrund eines gynäkologischen Tumors geplant war. Zu den untersuchten Faktoren gehörten die COVID-19-Pandemie, die Anzahl körperlicher Probleme, das Alter, der Allgemeinzustand, Tumorlokalisation und -stadium, Operation, Chemotherapie, Brachytherapie und ein anderes Malignom in der Vorgeschichte. Assoziationen zwischen den potenziellen Risikofaktoren und den sechs Aspekten von emotionalem Stress wurden mit dem Chi-Quadrat-Test oder dem exakten Fisher-Test untersucht. Nach Bonferroni-Korrektur wurden p-Werte <0,005 als signifikant angesehen (Alpha-Fehler 5%). Darüber hinaus zeigten p-Werte <0,06 Trends für Assoziationen zwischen Risikofaktoren und emotionalem Stress an.

Die Häufigkeit von Sorgen, Ängsten, Traurigkeit, Depression, Nervosität und Interessenverlust betrug 41%, 57%, 39%, 16%, 38% bzw. 20% (Abb. VII). Signifikante Assoziationen zwischen mindestens einem dieser Symptome und zwei möglichen Risikofaktoren (≥5 körperliche Probleme und keine vorherige Operation) wurden identifiziert. Ferner wurden Trends für Radiochemotherapie, einen weiteren Tumor in der Vorgeschichte, einen schlechteren Allgemeinzustand und jüngeres Alter beobachtet (Tabellen IV und V, Abb. VIII und IX). Die Prävalenz von emotionalem Stress vor der Strahlentherapie war auch bei Patientinnen mit gynäkologischen Malignomen in Bezug auf einige der sechs Aspekte hoch. Auch bei dieser Entität können Erkrankte mit Risikofaktoren von zeitnaher psychoonkologischer Hilfe profitieren.

Abb. VII. Die Prävalenz der sechs Aspekte von emotionalem Stress bei Patientinnen mit gynäkologischen Malignomen

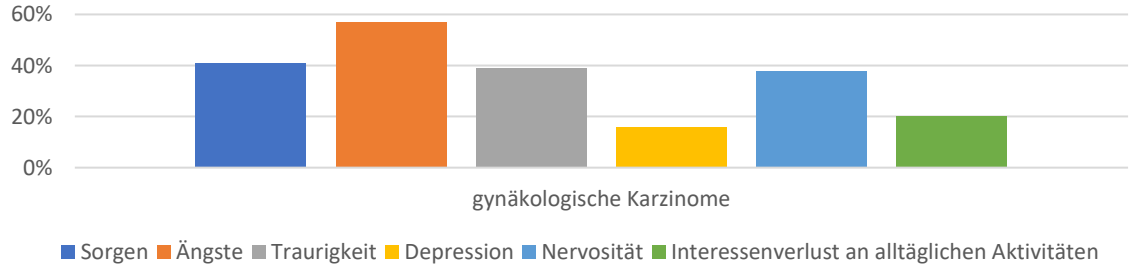


Tabelle IV. Signifikante Assoziationen bzw. Trends für Assoziationen zwischen Risikofaktoren und einzelnen Aspekten von emotionalem Stress bei Patientinnen mit gynäkologischen Malignomen

Aspekte von emotionalem Stress	Alter	Chemo. vor und/oder während RT	Anzahl physischer Probleme	Ja: N (%)	Nein: N (%)	p-Wert
Traurigkeit			0-4 (n=72) ≥5 (n=50)	15 (21) 32 (64)	57 (79) 18 (36)	**<0.0001**
Depression			0-4 (n=72) ≥5 (n=50)	3 (4) 16 (32)	69 (96) 34 (68)	**0.0001**
Interessenverlust an alltäglichen Aktivitäten			0-4 (n=72) ≥5 (n=50)	4 (6) 20 (40)	68 (94) 30 (60)	**<0.0001**
Angst		Nein (n=69) Ja (n=53)		33 (48) 36 (68)	36 (52) 17 (32)	0.026
Nervosität	≤65 Jahre (n=64) ≥66 Jahre (n=58)	Nein (n=69) Ja (n=53)		30 (47) 16 (28)	34 (53) 42 (72)	0.028

Tabelle V. Trend für eine Assoziation zwischen einem weiteren Malignom in der Vorgeschichte und Angst bei Patientinnen mit gynäkologischen Malignomen vor Strahlentherapie

Aspekte von emotionalem Stress	Malignom in der Vorgeschichte	Ja: n (%)	Nein: n (%)	p-Wert
Angst	Nein (n=107) Ja (n=15)	57 (53) 12 (80)	50 (47) 3 (20)	0.057

Abb. VIII. Signifikante Assoziation zwischen der Anzahl physischer Probleme und Traurigkeit, Depression sowie Verlust des Interesses an alltäglichen Aktivitäten bei Patientinnen mit gynäkologischen Malignomen vor Strahlentherapie

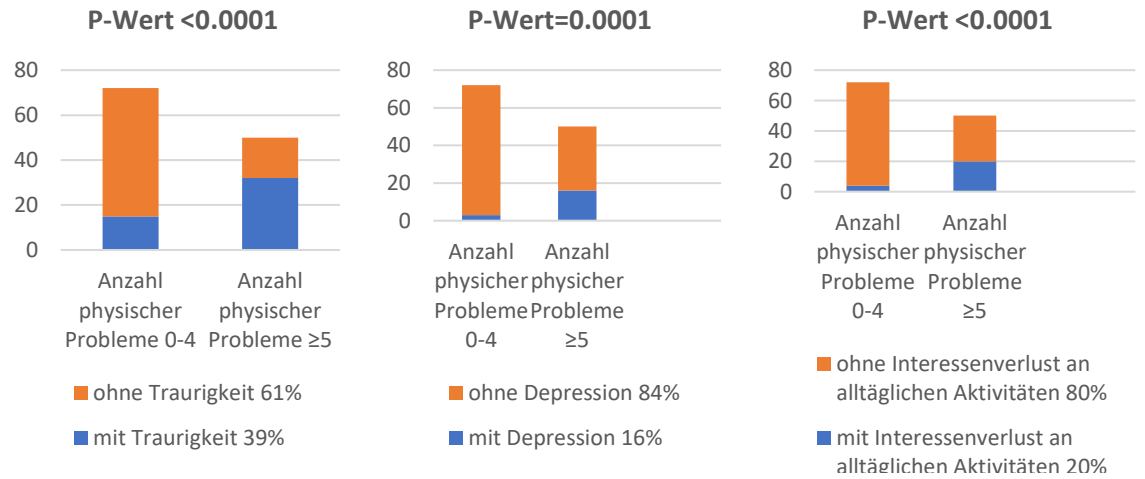
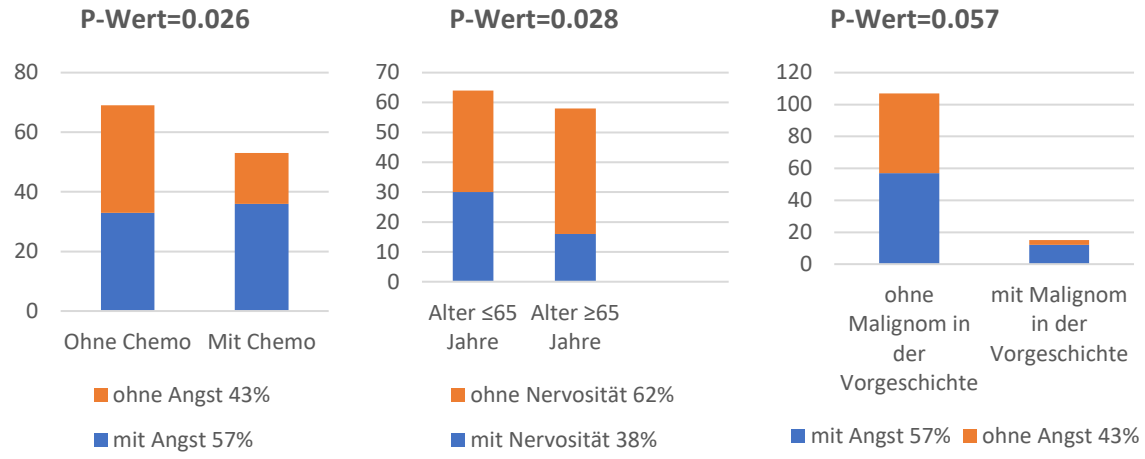


Abb. IX. Trends für Assoziationen zwischen Chemotherapie (vor und/oder während RT) bzw. Malignom in der Vorgeschichte und Angst sowie zwischen Alter und Nervosität bei Patientinnen mit gynäkologischen Malignomen vor Strahlentherapie



II.4 Emotionaler Stress bei Patient*innen mit malignen Gliomen vor Beginn der Bestrahlung (Publikation 4)

Eine Empfehlung zur Strahlentherapie bei Patient*innen mit malignen Gliomen kann emotionalen Stress auslösen. Prävalenz und Risikofaktoren dieser Komplikation wurden untersucht. Die Prävalenz der sechs emotionalen Probleme, die beim NCCN Distress-Thermometer abgefragt werden, wurden bei 103 Patient*innen ausgewertet, die einer Strahlentherapie mit oder ohne Chemotherapie bei einem WHO-Grad-II–IV-Gliom zugewiesen wurden. Elf potenzielle Risikofaktoren für emotionalen Stress wurden analysiert, darunter die Pandemie der Coronavirus-2019-Erkrankung (COVID-19) (vor vs. während der Pandemie), die Anzahl körperlicher Probleme (0-4 vs. ≥5), das Alter (≤59 vs. ≥60 Jahre), Geschlecht (weiblich vs. männlich), Karnofsky-Index (≤80 vs. >80), Anzahl der betroffenen Hirnareale (1 vs. ≥2), WHO-Grad (II-III vs. IV), Resektion vor RT (nein vs. ja), Radiochemotherapie (nein vs. ja), Behandlung mit Kortikosteroiden zum Zeitpunkt des Ausfüllens des Distress-Thermometers (nein vs. ja) und Vorgeschichte einer anderen malignen Erkrankung (nein vs. ja). Wie in den anderen Studien verwendeten wir für die statistischen Analysen den Chi-Quadrat-Test oder den exakten Fisher-Test. Nach der Bonferroni-Korrektur wurde ein p-Wert <0,0045 als signifikant angesehen (Alpha-Fehler 5%). Außerdem wurde ein p-Wert <0,05 als Hinweis auf einen Trend betrachtet. Mindestens ein emotionales Problem wurde von 76 Patient*innen (74%) angegeben. Die Prävalenz spezifischer emotionaler Probleme lag zwischen 23 % und 63 % (Abb. X). Es wurden Assoziationen zwischen ≥5 körperlichen Problemen und Sorgen (p=0,0010), Ängsten (p=0,0001), Traurigkeit (p=0,0023), Depression (p=0,0006) und Interessenverlust (p=0,0006) sowie zwischen einem Karnofsky-Index ≤80 und Depression (p=0,0002) gefunden. Ferner ergaben sich Trends für Assoziationen zwischen körperlichen Probleme

und Nervosität (p=0,040), Alter ≥60 Jahre und Depression (p=0,043) oder Interessenverlust (p=0,045), WHO Grad IV und Traurigkeit (p=0,042) und zwischen ≥2 betroffenen Regionen und Interessenverlust (p=0,022) (Tabellen VI und VII, Abb. XI und XII). Drei Viertel der Patient*innen mit einem Gliom litten vor der Strahlentherapie unter emotionalem Stress. Psychologische Unterstützung sollte sehr bald angeboten werden, insbesondere für Risikopatient*innen.

Abb. X. Die Prävalenz der sechs Aspekte von emotionalem Stress bei Patient*innen mit einem malignen Gliom

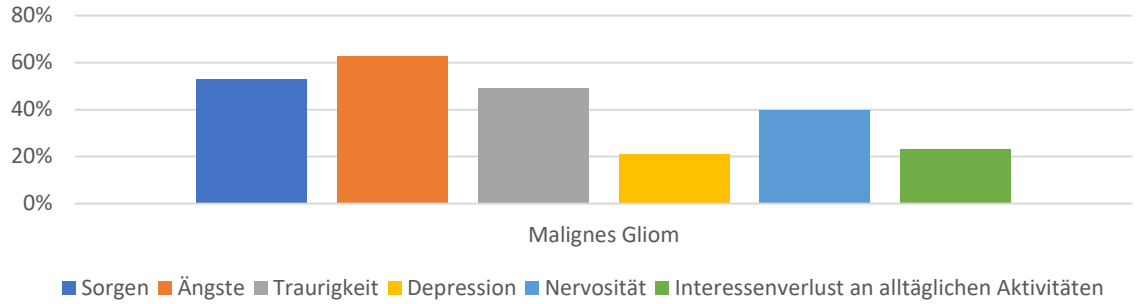


Tabelle VI. Signifikante Assoziationen bzw. Trends für Assoziationen zwischen Risikofaktoren und Aspekten von emotionalem Stress bei Patient*innen mit einem malignen Gliom

Aspekte von emotionalem Stress	Anzahl betroffener Hirnareale	Karnofsky-Index	Anzahl physischer Probleme	Ja: N (%)	Nein: N (%)	p-Wert
Angst			0-4 (*n*=53) ≥5 (*n*=50)	24 (45) 41 (82)	29 (55) 9 (18)	**0.0001**
Depression			0-4 (*n*=53) ≥5 (*n*=50)	4 (8) 18 (36)	49 (92) 32 (64)	**0.0006**
Depression		≤80 (*n*=48) >80 (*n*=55)		18 (38) 4 (7)	30 (63) 51 (93)	**0.0002**
Interessenverlust an alltäglichen Aktivitäten	1 (*n*=71) ≥2 (*n*=32)			12 (17) 12 (38)	59 (83) 20 (63)	0.022

Tabelle VII. Trend für Assoziation zwischen weiteren möglichen Risikofaktoren und einzelnen Aspekten von emotionalem Stress bei Patient*innen mit einem malignen Gliom

Aspekte von emotionalem Stress	Alter	WHO-Grad	Ja: N (%)	Nein: N (%)	p-Wert
Traurigkeit		II-III (*n*=23) IV (*n*=77)	7 (30) 42 (55)	16 (70) 35 (45)	0.042
Interessenverlust an alltäglichen Aktivitäten	≤59 Jahre (*n*=57) ≥60 Jahre (*n*=46)		9 (16) 15 (33)	48 (84) 31 (67)	0.045

Abb. XI. Signifikante Assoziationen zwischen möglichen Risikofaktoren und Aspekten von emotionalem Stress bei Patient*innen mit einem malignen Gliom

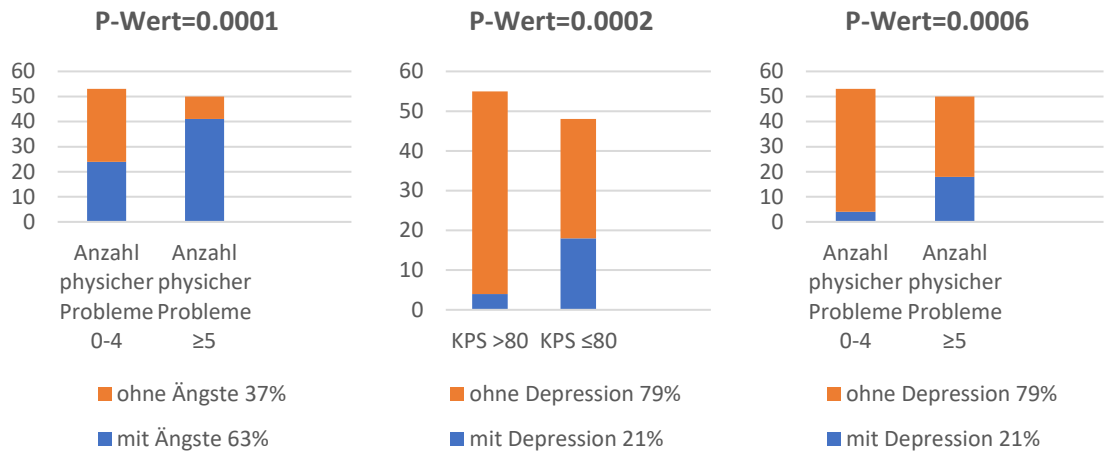
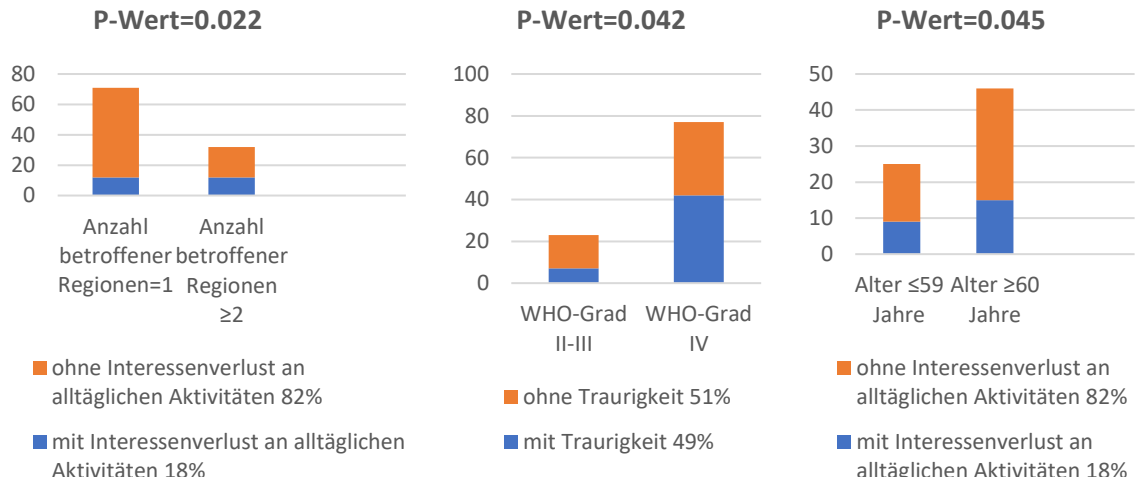


Abb. XII. Trends für Assoziationen zwischen weiteren möglichen Risikofaktoren und Aspekten von emotionalem Stress bei Patient*innen mit einem malignen Gliom



II.5 Prävalenz und Risikofaktoren für emotionalen Stress bei Patienten mit Prostatakarzinom vor Beginn einer perkutanen Strahlentherapie mit oder ohne Brachytherapie (Publikation 5)

Auch bei Patienten mit einem Prostatakarzinom kann die bevorstehende Strahlentherapie zu emotionalem Stress führen. Diese Studie evaluierte die Prävalenz und Risikofaktoren in einer retrospektiven Kohorte von 102 Patienten.

Diese Patienten, die aufgrund eines Prostatakarzinoms eine lokale oder loko-regionale Strahlentherapie erhielten, wurden retrospektiv hinsichtlich der sechs im NCCN Distress-Thermometer abgefragten emotionalen Probleme untersucht. Für jedes dieser Probleme wurden 13 patienten- und tumorbezogene Merkmale für mögliche Assoziationen untersucht. Zu diesen Merkmalen gehörten der zeitliche Bezug zur COVID-19-Pandemie (vor vs. während), die Anzahl körperlicher Probleme (0-1 vs. ≥2), das Alter zu Beginn der

EBRT (≤71 vs. ≥72 Jahre), Karnofsky-Index (≤90 vs. 100), primäres Tumorstadium (T1-2 vs. T3-4), Gleason-Score (≤7 vs. 8-9), prostataspezifisches Antigen (PSA) vor Strahlentherapie (<10 vs. ≥10 ng/ml), Operation (Prostatektomie) vor Strahlentherapie (nein vs. ja), Hormontherapie vor Strahlentherapie (nein vs. ja), Brachytherapie-Boost zusätzlich zur EBRT (nein vs. ja), Behandlungsvolumen (ohne vs. mit Lymphknoten/Beckenläsionen), Malignom in der Anamnese (nein vs. ja) und maligne Erkrankung in der Familienanamnese (nein vs. ja).

Mögliche Assoziationen zwischen diesen Merkmalen und den sechs emotionalen Problemen wurden mit dem Chi-Quadrat-Test oder dem exakten Fisher-Test analysiert. Nach Anwendung der Bonferroni-Korrektur wurden p-Werte <0,0038 als signifikant angesehen (Alpha-Fehler 5%). Außerdem wurden p-Werte <0,05 als Indikator für einen Trend betrachtet.

Die Prävalenz von Sorgen, Ängsten, Traurigkeit, Depression, Nervosität und Verlust des Interesses an alltäglichen Aktivitäten betrug 25 %, 27 %, 11 %, 11 %, 18 % bzw. 5 % (Abb. XIII). Eine größere Anzahl körperlicher Probleme war signifikant mit Sorgen (p=0,0037) und Ängsten (p<0,0001) assoziiert und zeigte Trends in Bezug auf Traurigkeit (p=0,011) und Depression (p=0,011). Es wurden ferner Trends für Assoziationen zwischen jüngerem Alter und Sorgen (p=0,021), fortgeschrittenem Primärtumorstadium und Ängsten (p=0,025), einer anderen malignen Erkrankung in der Vorgeschichte der Patienten und Nervosität (p=0,035) und zwischen alleiniger perkutaner Strahlentherapie ohne Brachytherapie und Ängsten (p=0,042) oder Nervosität (p=0,037) beobachtet (Tabellen VIII und IX, Abb. XIV und XV). Obwohl die Prävalenz für die Aspekte von emotionalem Stress niedriger als bei anderen Tumorentitäten war, können auch Patienten mit einem Prostatakarzinom, insbesondere bei Vorliegen von Risikofaktoren, von frühzeitiger psychologischer Unterstützung profitieren.

Abb. XIII. Die Prävalenz der sechs Aspekte von emotionalem Stress bei Patienten mit einem Prostatakarzinom

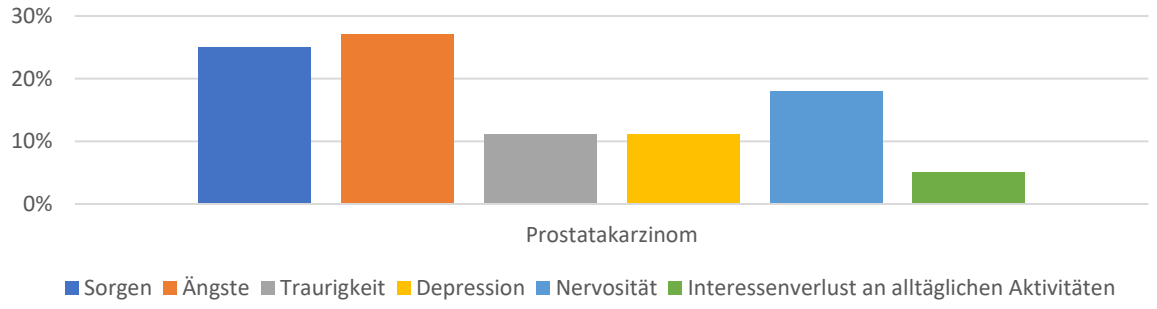


Tabelle VIII. Signifikante Assoziationen bzw. Trends für Assoziationen zwischen Risikofaktoren und Aspekten von emotionalem Stress bei Patienten mit einem Prostatakarzinom

Aspekte von emotionalem Stress	T-Stadium	Alter	Anzahl physischer Probleme	Ja: N (%)	Nein: N (%)	p-Wert
Angst			0-1 (*n*=46) ≥2 (*n*=56)	3 (7) 25 (45)	43 (93) 31 (55)	**<0.0001**
Sorgen			0-1 (*n*=46) ≥2 (*n*=56)	5 (11) 20 (36)	41 (89) 36 (64)	**0.0037**
Sorge		≤71 Jahre (*n*=53) ≥72 Jahre (*n*=49)		18 (34) 7 (14)	35 (66) 42 (86)	0.021
Angst	1-2 (*n*=79) 3-4 (*n*=22)			17 (22) 10 (45)	62 (78) 12 (55)	0.025

Tabelle IX. Trends für Assoziationen zwischen weiteren Risikofaktoren und Aspekten von emotionalem Stress bei Patienten mit einem Prostatakarzinom

Aspekte von emotionalem Stress	Brachytherapie-Boost	Malignom in der Vorgeschichte	Ja: N (%)	Nein: N (%)	p-Wert
Nervosität		Nein (*n*=89) Ja (*n*=13)	13 (15) 5 (38)	76 (85) 8 (62)	0.035
Angst	Nein (*n*=76) Ja (*n*=26)		25 (33) 3 (12)	51 (67) 23 (88)	0.042

Abb. XIV. Signifikante Assoziationen bzw. Trends für Assoziationen zwischen Risikofaktoren und Aspekten von emotionalem Stress bei Patienten mit einem Prostatakarzinom

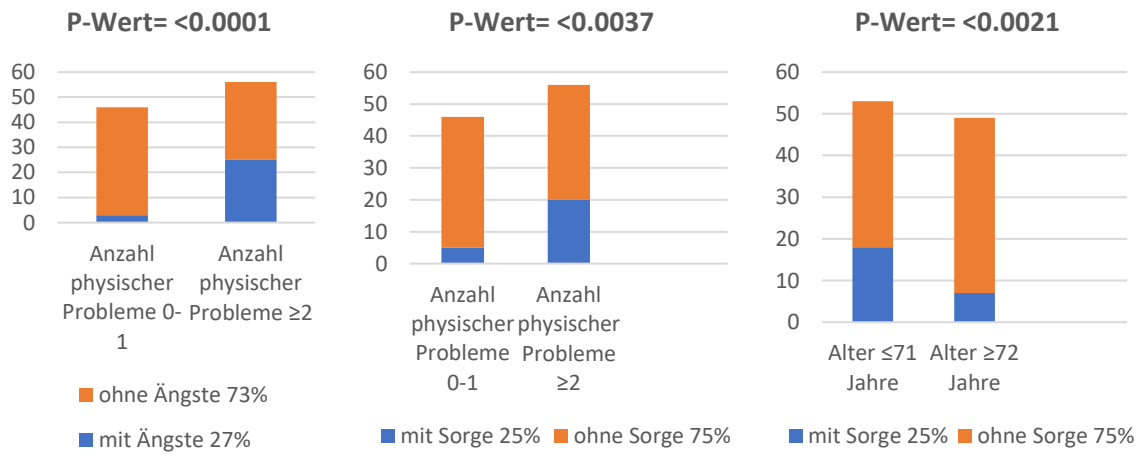
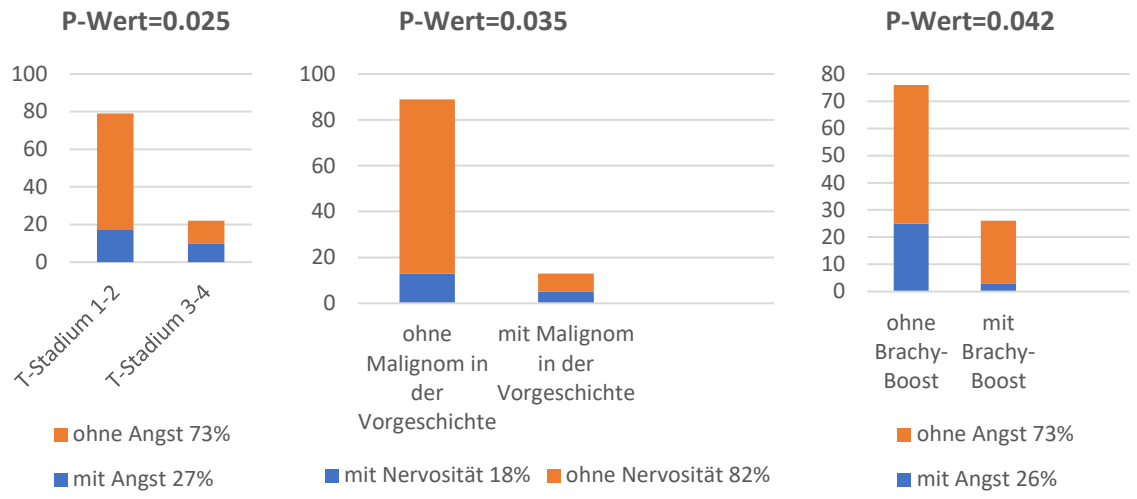


Abb. XV. Trends für Assoziationen zwischen weiteren Risikofaktoren und Aspekten von emotionalem Stress bei Patienten mit einem Prostatakarzinom



II.6 Emotionaler Stress vor einer Radiochemotherapie bei Rektum- oder Analkarzinomen (Publikation 6)

Es wurde berichtet, dass eine bevorstehende Radiochemotherapie bei Patient*innen mit Rektumkarzinom psychosoziale Belastungen verursacht. Diese Studie liefert zusätzliche Daten zu Prävalenz und Risikofaktoren von emotionalem Stress bei Patient*innen, die wegen eines Rektum- oder Analkarzinoms eine Radiochemotherapie erhalten haben oder erhalten sollten.

Die Daten von 64 Patient*innen wurden retrospektiv in Bezug auf emotionalen Stress vor der Behandlung analysiert. 45 Patient*innen hatten ein lokal fortgeschrittenes Rektumkarzinom und 19 Patient*innen ein Analkarzinom. In der gesamten Kohorte wurden 12 Faktoren hinsichtlich möglicher Assoziationen mit emotionalem Stress (NCCN Distress-Thermometer vor Therapiebeginn analysiert. Zu diesen Faktoren gehörten die Zeit der COVID-19-Pandemie (vor vs. während), die Anzahl körperlicher Probleme (0-3 vs. ≥4), Alter (≤67 vs. ≥68 Jahre, Median = 68 Jahre), Geschlecht (weiblich vs. männlich), Karnofsky-Index (≤80 vs. ≥90), Art des Primärtumors (Rektum- vs. Analkarzinom), Tumorkategorie (T2-3 vs. T4), Nodalstatus (negativ vs. positiv), Fernmetastasen (nein vs. ja), Operation vor RT (nein vs. ja), weiteres Malignom in der Eigenanamnese (nein vs. ja) oder Malignom in der Familienanamnese (nein vs. ja).

Für die statistische Analysen wurden wiederum der Chi-Quadrat-Test und der exakte Test nach Fisher verwendet. Nach Anwendung der Bonferroni-Korrektur wurden p-Werte

<0,0042 als signifikant angesehen (Alpha-Fehler 5%). Bei p<0,01 wurden die Ergebnisse als starker Trend und bei p<0,05 als Trend gewertet.

Es berichteten 31 %, 47 %, 33 %, 11 %, 47 % bzw. 19 % der Patient*innen über Sorgen, Ängste, Traurigkeit, Depression, Nervosität und Verlust des Interesses an alltäglichen Aktivitäten (Abb. XVI). Eine höhere Anzahl körperlicher Probleme war mit Ängsten (p=0,0030) und Verlust des Interesses an alltäglichen Aktivitäten (p=0,0021) assoziiert. Starke Trends wurden für Assoziationen zwischen weiblichem Geschlecht und Traurigkeit (p=0,0098) und zwischen niedrigerem Karnofsky-Index und Sorgen (p=0,0068) oder Ängsten (p=0,0064) beobachtet (Tabelle X, Abb. XVI und XVII). Ein erheblicher Anteil der Patient*innen berichtete vor der Radiochemotherapie bei Rektum- oder Analkarzinom über emotionalen Stress. Wie bei anderen Tumorentitäten können Risikopatient*innen von einer frühen psychoonkologischen Unterstützung profitieren.

Abb. XVI. Die Prävalenz der sechs Aspekte von emotionalem Stress bei Patient*innen mit einem Rektum- oder Analkarzinom

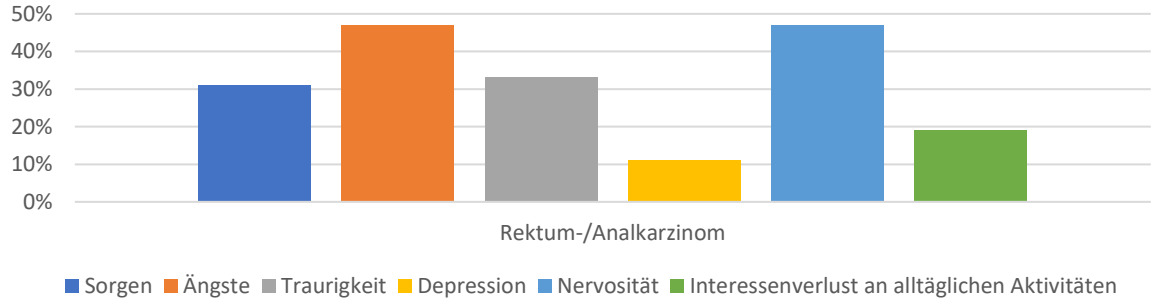
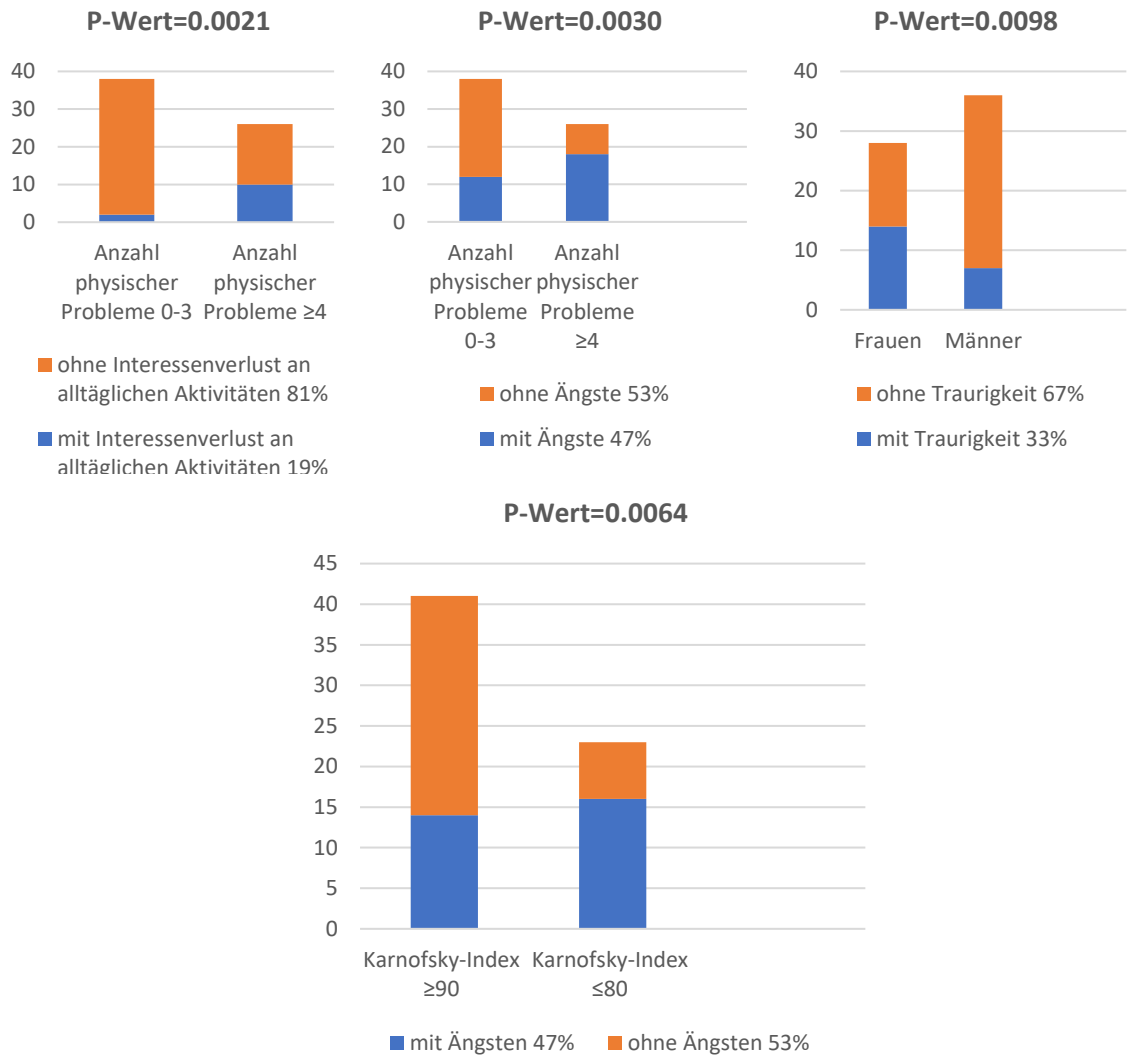


Table X. Signifikante Assoziationen bzw. Trends für Assoziationen zwischen Risikofaktoren und Aspekten von emotionalem Stress bei Patienten mit einem Rektum- oder Analkarzinom

Kategorien des Emotionalen Disstress	Karnofsky-Index	Geschlecht	Anzahl physischer Probleme	Ja: N (%)	Nein: N (%)	p-Wert
Interessenverlust an alltäglichen Aktivitäten			0-3 (*n*=38) ≥4 (*n*=26)	2 (5) 10 (38)	36 (95) 16 (62)	**0.0021**
Ängste			0-3 (*n*=38) ≥4 (*n*=26)	12 (32) 18 (69)	26 (68) 8 (31)	**0.0030**
Traurigkeit		weiblich (*n*=28) männlich (*n*=36)		14 (50) 7 (19)	14 (50) 29 (81)	0.0098
Ängste	≤80 (*n*=23) ≥90 (*n*=41)			16 (70) 14 (34)	7 (30) 27 (66)	0.0064

Abb. XVII. Signifikante Assoziationen bzw. Trends für Assoziationen zwischen Risikofaktoren und Aspekten von emotionalem Stress bei Patient*innen mit einem Rektum- oder Analkarzinom



III. Diskussion:

III.1 Emotionaler Stress vor Radiochemotherapie oder alleiniger Strahlentherapie von Kopf-Hals-Karzinomen (Publikation 1)

Da Strahlentherapie und Radiochemotherapie von Kopf-Hals-Karzinomen häufig zu belastenden Nebenwirkungen führen, kann es bei Erkrankten, die einer dieser Behandlungen zugewiesen werden, zu emotionalem Stress kommen (26,55,79,98,99,103,129,119,137). In früheren Studien hatten 8-58 % der Patient*innen Depressionen und 20-40 % Angst vor der Strahlenbehandlung (16,36,82,83,128). Darüber hinaus gaben in der Studie von Lewis et al. 56 % der Patient*innen mit Kopf-Hals-Karzinomen vor einer Strahlentherapie erhebliche nicht näher spezifizierte Belastungen an (58). In einer weiteren Studie berichteten 44 von 103 (43%) Patient*innen mit Kopf-Hals-Karzinomen, die einer Radio-(Chemo-)Therapie zugewiesen wurden, von Schlafstörungen, die signifikant mit der Anzahl emotionaler Probleme assoziiert waren (p=0,001) (92). In unserer aktuellen Studie war der Anteil der Patient*innen, die mindestens ein emotionales Problem hatten, höher als die Raten von Depressionen, Angstzuständen und allgemeinem Stress in früheren Studien (16,36,58,82,83,128). Die spezifische Prävalenz der sechs untersuchten emotionalen Probleme lag in unserer Studie jedoch innerhalb des zuvor für Depression und Angst berichteten Bereichs (16,36,82,83,128).

Bezüglich der Risikofaktoren ergaben sich in dieser Studie signifikante Assoziationen zwischen der Anzahl körperlicher Beschwerden bzw. weiblichem Geschlecht mit mindestens einem emotionalen Problem. Bei der Interpretation der Ergebnisse sollte das retrospektive Design dieser Studie berücksichtigt werden. Unsere Ergebnisse entsprechen jedoch denen früherer Studien überein. Neilson et al. fanden heraus, dass Depression und Ängste mit der Anzahl körperlicher Symptome zusammenhingen (82). In der Studie von Gosak et al. wurden Depressionen und Angstzustände häufiger bei Patient*innen mit Kachexie, die in der Regel mit einem schlechteren Allgemeinzustand einhergeht, festgestellt (36). In einer Studie, die die psychische Belastung im Verlauf der Strahlentherapie bei Kopf-Hals-Karzinomen und ihren Betreuungspersonen untersuchte, waren körperliche Beschwerden, Schlafstörungen, Schmerzen, Mundsoor, Probleme beim Essen und Müdigkeit die am häufigsten genannten Ursachen für Stress (8). In einer anderen Studie, in der der Stress nach einer Strahlentherapie untersucht wurde, war der körperliche Allgemeinzustand ein signifikanter Prädiktor für Angstzustände (69). Assoziationen zwischen weiblichem Geschlecht und dem Auftreten von Depressionen und Angstintensität wurden in der Studie von Wang et al. gefunden, die Patient*innen mit Nasopharynxkarzinom untersuchten, die einer Strahlentherapie zugewiesen wurden (128). In Bezug auf die prognostische Bedeutung eines schlechteren Allgemeinzustandes wurde

in unserer vorherigen Studie ein Zusammenhang zwischen einem niedrigeren Karnofsky-Index und der Prävalenz von Schlafstörungen gefunden (92). Außerdem berichteten Gunn et al., dass ein schlechterer Allgemeinzustand mit einer höheren Symptombelastung einschließlich Stress vor der Strahlentherapie von Kopf-Hals-Tumoren korreliert war (37). Im Gegensatz zu den oben genannten Risikofaktoren war die COVID-19-Pandemie nicht mit der Prävalenz von emotionalem Stress assoziiert. Dieses Ergebnis stimmt mit einer vorangegangenen Querschnittsstudie aus Brasilien überein, die während der Pandemie bei Patient*innen mit Kopf-Hals-Karzinomen unter Strahlentherapie keinen Anstieg der Belastung feststellte (108).

III.2 Prävalenz und Risikofaktoren für emotionalen Stress vor einer Strahlentherapie bei Patient*innen mit einem Lungenkarzinom (Publikation 2)

Auch die Strahlentherapie und Radiochemotherapie bei Lungenkarzinomen können relevante akute und späte Toxizitäten verursachen (39,90,104,126,130). Daher kann auch bei diesen Patient*innen die Auswahl für eine derartige Behandlung zu erheblichem emotionalem Stress führen. In der Literatur variiert die Prävalenz von emotionalem Stress vor der Behandlung bei Patient*innen mit Lungenkarzinom (32,70,124). In der randomisierten Studie von Falk et al. beim Vergleich einer sofortigen mit einer verzögerten palliativen Strahlentherapie bei 230 Patient*innen mit inoperablem NSCLC gaben zu Studienbeginn 12% derjenigen, die sich einer sofortigen Behandlung unterzogen, bzw. 11% derjenigen, die sich einer verzögerten Behandlung unterzogen, relevante Ängste an (32). Sehr gering ausgeprägte Ängste wurden von weiteren 24% bzw. 16% der Patient*innen berichtet, was Gesamtraten von 36% bzw. 27% bedeutete. Die Gesamtraten hinsichtlich Depressionen betrugen 21% bzw. 20%. In einer weiteren randomisierten Studie mit 509 Patient*innen, die 2 × 8,5 Gy mit 13 × 3 Gy bei inoperablem NSCLC verglich, berichteten 17,8% bzw. 17,1% der Patient*innen vor der Strahlentherapie über psychische Belastungen (70). In einer prospektiven Kohortenstudie mit 191 Patient*innen betrug die Prävalenz von Ängsten vor Strahlentherapie 21% bei jüngeren (43-65 Jahre) bzw. 12 % bei älteren (75-89 Jahre) Patient*innen. Die Prävalenz von Depressionen betrugen 21% in beiden Altersgruppen (124). Darüber hinaus wurde in einer Querschnittsstudie aus China von 53,5 % bzw. 65,5 % der Patient*innen, die eine Strahlentherapie erhielten, Ängste bzw. Depressionen berichtet (133). Angesichts der großen Spannweite hinsichtlich der Raten von emotionalem Stress (Ängste und Depressionen) sind zusätzliche Studien erforderlich, um die Prävalenz dieser Komplikation genauer definieren zu können. In der vorliegenden Studie wurde die Prävalenz der sechs emotionalen Probleme untersucht, die im NCCN Distress-Thermometer enthalten sind (42). Die Prävalenz lag zwischen 15% und 38%.

Diese Raten waren ähnlich wie die Gesamtraten von Angst und Depression in der randomisierten Studie von Falk et al. (32) und die Raten bei jüngeren Patient*innen in der prospektiven Beobachtungsstudie von Turner et al. (124). Auch beim Vergleich der ≥ 70-jährigen Patient*innen unserer Studie mit den älteren Patient*innen der Studie von Turner et al. waren die Raten emotionaler Probleme ähnlich (7–21% versus 12–21%) (124). Darüber hinaus berichteten 65 % unserer Patient*innen von mindestens einem emotionalen Problem. Diese Häufigkeit war ähnlich wie die Raten von Angst und Depression, die in einer früheren Querschnittsstudie beobachtet wurden (133).

Neben der Prävalenz von emotionalem Stress untersuchten wir mögliche Risikofaktoren. Das Auftreten von mindestens einem emotionalen Problem war signifikant mit einer größeren Anzahl körperlicher Probleme, jüngerem Alter und weiblichem Geschlecht assoziiert. Darüber hinaus wurde ein Trend für eine Assoziation mit gleichzeitiger Radiochemotherapie gefunden. Die Tatsache, dass körperliche Probleme und Symptome die psychische Belastung bei Patient*innen mit einem Lungenkarzinom erhöhen, wurde zuvor für verschiedene Situationen beschrieben (30,64,68,74). Darüber hinaus wurde in unserer vorherigen Studie eine größere Anzahl körperlicher Probleme als signifikanter Risikofaktor für Schlafstörungen identifiziert (94). Assoziationen zwischen emotionalem Disstress und jüngerem Alter wurden auch in anderen Studien gefunden. In der prospektiven Beobachtungsstudie von Turner et al. hatten jüngere Patient*innen generell mehr Bedenken, und die Angstprävalenz war höher (124). In der Querschnittsstudie von Yan et al. waren Patient*innen mit Angst und Depression signifikant jünger als Patient*innen ohne diese Probleme (133). Darüber hinaus war in der Studie von Mazanec et al., die Prädiktoren der psychosozialen Anpassung nach Strahlentherapie bei Patient*innen mit Lungen-, Brust- oder Prostatakarzinom untersuchte, ein jüngeres Alter mit einer schlechteren Anpassung assoziiert (75). Ein Einfluss des Geschlechts auf den emotionalen Disstress wurde auch in früheren Studien bei Patient*innen mit einem Lungenkarzinom festgestellt. In der Studie von Yan et al. litten Frauen häufiger unter Angstzuständen (51% vs. 40%, p=0,060) und Depressionen (64% vs. 54%, p=0,067) (133). Der Trend zu einem Zusammenhang zwischen emotionalem Disstress und gleichzeitiger Chemotherapie lässt sich dadurch erklären, dass die Hinzunahme einer Chemotherapie zur Strahlentherapie die behandlungsbedingten akuten Toxizitäten signifikant erhöht (17,22,47,49,50). Obwohl die Ergebnisse unserer Studie mit denen früherer Studien übereinstimmen oder gut erklärt werden können, ist der retrospektive Charakter der Daten (Risiko für Selektionsbias) bei deren Interpretation zu berücksichtigen.

III.3 Prätherapeutischer emotionaler Stress bei Patientinnen, die eine Strahlentherapie bei gynäkologischen Malignomen erhalten haben (Publikation 3)

Gynäkologische Malignome sind die zweithäufigste Gruppe bösartiger Tumoren bei Frauen (116). Viele dieser Patientinnen werden mit EBRT, BT oder einer Kombination beider Techniken behandelt. Eine Empfehlung zur Strahlentherapie kann auch in dieser Gruppe zu emotionalem Disstress führen. Es fehlt an Studien, die sich auf die Prävalenz und Risikofaktoren vom emotionalen Disstress vor einer Strahlentherapie bei gynäkologischen Tumoren konzentrieren. Diese Studie untersuchte beide Aspekte in einer Kohorte von 122 Patientinnen, die wegen Endometrium-, Zervix-, Vaginal- oder Vulvakarzinom bestrahlt wurden oder werden sollten. Wiederum wurde das NCCN Distress-Thermometer verwendet (42). Die Häufigkeit der sechs emotionalen Probleme des Distress-Thermometers lag zwischen 16% und 57% und unterschieden sich nicht wesentlich von der Stressprävalenz im Allgemeinen in früheren Studien bei Patientinnen mit gynäkologischen Tumoren (20% bis 50%) oder Patientinnen mit Zervixkarzinom während einer Strahlentherapie (23% bis 69%) (48, 60).

In dieser Studie wurden signifikante Assoziationen für mehr körperliche Probleme und Inoperabilität mit mindestens einem emotionalen Problem gefunden. Eine Korrelation zwischen körperlichen Problemen und emotionalem Stress wurde zuvor in anderen Studien mit gynäkologischen Tumoren beobachtet (21, 40). Darüber hinaus war in einer Studie die Prävalenz von Schlafproblemen signifikant mit einer größeren Anzahl von körperlichen Problemen assoziiert (93). Das Ergebnis, dass Inoperabilität mit mehr emotionalem Stress verbunden war, kann dadurch erklärt werden, dass die Mehrheit dieser Patientinnen eine fortgeschrittene Krankheit hatte und Inoperabilität oft mit einer schlechteren Prognose verbunden ist (38).

Darüber hinaus wurden Trends für Assoziationen zwischen emotionalem Stress und zusätzlicher Chemotherapie, einem weiteren Tumor in der Anamnese, schlechterem Allgemeinzustand oder jüngerem Alter beobachtet. Der Trend bezüglich der zusätzlichen Chemotherapie lässt sich durch die erhöhte Toxizität der Radiochemotherapie im Vergleich zur alleinigen Strahlentherapie erklären (23,24,31,61,71,88,123,135). Ein weiterer Tumor in der Vorgeschichte kann den emotionalen Stress verstärken (95). Darüber hinaus bedeutet die Angst vor einem Fortschreiten der Erkrankung für viele Patientinnen eine erhebliche Belastung (38). Assoziationen zwischen einem schlechteren Karnofsky-Index und einer höheren emotionalen Belastung wurden zuvor in einer großen retrospektiven Studie bei Patientinnen mit Brustkrebs und gynäkologischen Tumoren gefunden (63).

Gleiches gilt für die Korrelation zwischen jüngerem Alter und emotionalem Stress (54,63,95,122,125).

III.4 Emotionaler Stress bei Patient*innen mit malignen Gliomen vor Beginn der Bestrahlung (Publikation 4)

Die Diagnose und Behandlung von malignen Hirntumoren können zu erheblichen emotionalen und psychischen Belastungen führen. Die Prävalenz vom emotionalen Stress weist je nach Situation der Patient*innen erhebliche Unterschiede auf. In einer prospektiven Beobachtungsstudie mit 149 Patient*innen mit einem niedrig-gradigen Gliom litten 20,8% der Patient*innen an erhöhtem Stress (59). In einer Pilotstudie mit 32 Patient*innen mit hochgradigem Gliom und 31 Betreuer*innen berichteten 60% der Patient*innen über klinisch signifikante Belastungen (87). In einer anderen Studie, die sowohl Patient*innen als auch Betreuer*innen berücksichtigte, wiesen 37,5% der Patient*innen mit einem primären Hirntumor zum Zeitpunkt der Diagnose einen Distress-Score über dem Cut-off-Wert auf (121). Die Studie von Randazzo et al. verwendete das NCCN Distress-Thermometer, um die psychosoziale Belastung bei 829 Patient*innen mit einem primären Hirntumor zu bewerten (42,105). Die Prävalenz von Sorgen, Ängsten und Nervosität betrug 29,4%, 17,5% bzw. 22,4%. In der Studie von Mainio et al. berichteten 35 % der Patient*innen über eine Depression vor der Resektion eines primären Hirntumors (73). Rooney et al. bewerteten fünf Qualitäten von emotionalem Stress zu verschiedenen Zeitpunkten (109). Kurz nach Beginn der Strahlen- oder Chemotherapie, wurden Sorgen, Ängste, Traurigkeit, Depression und Nervosität von 29%, 14%, 15%, 6% bzw. 19% der Patient*innen angegeben. Darüber hinaus wurde in einer systematischen Übersichtsarbeit, die 92 Artikel berücksichtigte, eine Prävalenz von 60,9% für einen emotionalen Stress gefunden (136). Bisher konzentrierte sich keine Studie speziell auf die Prävalenz von emotionalem Stress vor einer Strahlentherapie oder Chemotherapie bei malignen Gliomen. In unserer Studie zu dieser Situation gaben 74% der Patient*innen mindestens ein emotionales Problem an. Darüber hinaus war die Prävalenz der sechs Aspekte von emotionalem Stress höher als in den Studien von Randazzo et al. und Rooney et al. (105, 109). Diese Ergebnisse unterstützen die Hypothese, dass eine anstehende Strahlentherapie für Patient*innen mit malignem Gliom emotional besonders belastend ist.

In unserer Studie war emotionaler Disstress signifikant mit einer größeren Anzahl körperlicher Probleme und einem niedrigeren Karnofsky-Index assoziiert. Darüber hinaus wurden Trends für höheres Alter (≥60 Jahre), Glioblastoma multiforme und Beteiligung von ≥2 Arealen gefunden. Die prognostische Rolle körperlicher Probleme wurde bereits in anderen Studien beschrieben. In der Studie von Osoba et al. war ein sich verschlechternder

neurologischer Status mit einer Zunahme des emotionalen Stresses bei Patient*innen mit Hirntumoren verbunden (86). Darüber hinaus korrelierte die Anzahl der körperlichen Probleme mit dem Auftreten von Schlafstörungen (53). Assoziationen zwischen einem schlechteren Karnofsky-Index und einer höheren Stress-Prävalenz wurden zuvor von Mainio et al. berichtet (73). Darüber hinaus fanden Rooney et al. einen signifikanten Zusammenhang zwischen einem Karnofsky-Index ≤70 und depressiven Störungen kurz nach Beginn der Strahlentherapie bei zerebralem Gliom (109). In der Studie von Abete-Fornara et al. war die Wahrscheinlichkeit schwerer psychischer Belastungen bei Patient*innen mit Hirntumoren signifikant mit höherem Lebensalter assoziiert (1). Dass Stress mit aggressiveren Gliomen (höhere WHO-Grade) korreliert, wurde bereits von Trad et al. und Leonetti et al. beschrieben (57,121). Ein Zusammenhang zwischen emotionalem Stress und der Beteiligung von ≥2 Arealen kann durch die in diesen Fällen schlechtere Überlebensprognose erklärt werden (101).

III.5 Prävalenz und Risikofaktoren für emotionalen Stress bei Patienten mit Prostatakarzinom vor Beginn einer perkutanen Strahlentherapie mit oder ohne Brachytherapie (Publikation 5)

Die Strahlentherapie des Prostatakarzinoms kann mit urogenitalen und gastrointestinalen Nebenwirkungen verbunden sein und daher zu emotionalem Disstress führen, der mit dem Distress-Thermometer des National Comprehensive Cancer Network (48) beurteilt werden kann. In der vorliegenden Studie lag die Prävalenz der mit dem NCCN Distress-Thermometer erfassten emotionalen Probleme zwischen 5% und 27%. Diese Raten ähneln denen, die in anderen Prostatakarzinom-Studien gefunden wurden. In einer retrospektiven Studie mit 861 Männern, die in den letzten sieben Jahren eine EBRT, Brachytherapie oder radikale Prostatektomie erhalten hatten, lag die Prävalenz von Angst und Depression bei 25% bzw. 17% (41). In einer anderen Studie, die das Distress-Thermometer verwendete, gaben weniger als 20% der Patienten Werte von ≥4 (Cut-off für signifikanten Stress) an (65). Darüber hinaus wurden prätherapeutische Schlafstörungen, die eine Folge von emotionalem Stress sein können, bei 21% der Patienten berichtet, die einer Strahlentherapie bei Prostatakarzinom zugewiesen wurden (52).

In unserer Studie war die Prävalenz von Sorgen und Ängsten signifikant mit einer größeren Anzahl von körperlichen Problemen assoziiert. Darüber hinaus zeigte die Anzahl der körperlichen Probleme Trends für Assoziationen mit Traurigkeit und Depression. Diese Ergebnisse stimmen mit denen früherer Studien bei Patienten mit einem Prostatakarzinom in anderen Situationen überein. In einer Studie, die Daten von 1148 Patienten aus einer früheren prospektiven Studie verwendete, die eine Operation (63%) oder eine

Strahlentherapie (37%) erhalten hatten, berichteten Patienten mit stärker eingeschränkter Harn-, Darm- und Sexualfunktion über größeren emotionalen Stress (85). In einer Studie, die Basisdaten einer randomisierten Studie analysierte, die verschiedene Behandlungen für Prostatakarzinom umfasste, waren Probleme im Zusammenhang mit dem täglichen Leben signifikant mit globalem Stress verbunden ($p<0,0005$) (65). In einer weiteren prospektiven Studie, wurden psychischer Stress, Depression und Angstzustände mit Harnwegserkrankungen und einer Verschlechterung der Sexualfunktion in Verbindung gebracht (113). Die Ergebnisse früherer Studien wurden durch einen Übersichtsartikel unter Berücksichtigung von 18 Original- und anderen Übersichtsartikeln untergestützt (72). Zusätzlich zum Einfluss der Anzahl körperlicher Probleme auf die Entwicklung vom emotionalen Disstress zeigte die vorliegende Studie Trends für jüngeres Alter, fortgeschrittenes Primärtumorstadium, Malignom(e) in der Vorgeschichte und Bestrahlung ohne Brachytherapie. Jüngeres Alter wurde zuvor als Risikofaktor für Angstzustände bei Langzeitüberlebenden nach radikaler Prostatektomie identifiziert (76). Ein fortgeschrittenes Primärtumorstadium ist mit einem Rezidivrisiko verbunden, was zu erhöhtem emotionalem Stress führen kann (77,114,127). Ähnlich wie die Angst vor einem Rezidiv kann ein weiterer Tumor in der Vorgeschichte zu mehr emotionalem Stress führen. Ein weiteres Ergebnis der vorliegenden Studie war ein Trend für eine Assoziation zwischen EBRT ohne Brachytherapie und einer höheren Prävalenz emotionaler Probleme. Dieser Befund kann durch die Tatsache erklärt werden, dass die EBRT plus Brachytherapie-Boost mit einer geringeren Toxizität einhergeht als die alleinige EBRT (84). Obwohl die Ergebnisse der vorliegenden Studie mit denen früherer Studien übereinstimmen oderausreichend erklärt werden können, müssen das retrospektive Design und das Risiko eines versteckten Selektionsbias bei der Interpretation der Ergebnisse berücksichtigt werden.

III.6 Emotionaler Stress vor einer Radiochemotherapie bei Rektum- oder Analkarzinomen (Publikation 6)

Auch die Radiochemotherapie bei Rektum- oder Analkarzinomen kann mit erheblicher Toxizität und emotionalem Stress für die Patient*innen einhergehen (18). In einer vorherigen Studie berichteten 42,9% der Patient*innen mit Rektum- oder Analkarzinom über Schlafstörungen vor ihrer Radiochemotherapie (91). Diese Störungen wurden durch mehrere Faktoren ausgelöst, unter anderem durch emotionale Probleme. In der vorliegenden Studie lagen die Häufigkeiten der sechs untersuchten emotionalen Probleme zwischen 11% und 47%. In anderen Studien, die psychischen Stress einschließlich emotionaler Probleme nach der Behandlung von Rektumkarzinomen untersuchten, lag die Prävalenz zwischen 36% und 43% (35,89,115). Die Zahlen zeigen, dass emotionaler Stress für diese Patient*innen ein relevantes Problem darstellt.

In der vorliegenden Studie war emotionaler Stress signifikant mit einer größeren Anzahl körperlicher Probleme assoziiert. Darüber hinaus wurden Trends für Assoziationen mit emotionalen Problemen für das weibliche Geschlecht und einen niedrigeren Karnofsky-Index gefunden. Assoziationen zwischen körperlichen Problemen und emotionalem Stress wurden bereits in anderen Studien bei Patient*innen mit Rektum- oder Analkarzinom beschrieben. In der Studie von Benedict et al. mit 70 Patient*innen, die wegen Rektum- oder Analkarzinom behandelt wurden, korrelierten Depressionen mit schweren Diarrhoen und anderen gastrointestinalen Symptomen und Angst mit gastrointestinalen Symptomen (11). In einer anderen Studie wirkte sich die Darmfunktionsstörung nach Resektion eines Rektumkarzinoms, insbesondere die Angst vor Inkontinenz, negativ auf die soziale Funktion der Patient*innen aus (28). In der Studie von Chambers et al. waren ein permanentes Stoma und Müdigkeit Risikofaktoren für eine ausgeprägtere psychische Belastung (14). Potenzielle Assoziationen zwischen weiblichem Geschlecht und emotionalem Stress wurden ebenfalls zuvor berichtet. In der Studie von Bencova et al. waren bei Patient*innen mit Rektumkarzinom vor geplanter, neoadjuvanter Radiochemotherapie psychosoziale Probleme bei Frauen stärker ausgeprägt (10). Wie bei allen Studien im Rahmen dieser Dissertation muss das retrospektive Studiendesign bei der Interpretation der Ergebnisse berücksichtigt werden.

IV. Zusammenfassung und Ausblick:

Die Prävalenz der sechs Aspekte von emotionalem Stress bzw. emotionalen Probleme, die mit dem NCCN Distress-Thermometer erfasst werden, war bei den untersuchten Tumorentitäten unterschiedlich. Die niedrigste Prävalenz wurde bei Patienten mit einem Prostatakarzinom gefunden (5-27%), die höchste Prävalenz bei Patient*innen mit einem malignen Gliom (21-63%). Auch die Risikofaktoren für emotionalen Stress unterschieden sich bei den sechs Tumorentitäten, bis auf die höhere Anzahl körperlicher Probleme. Dieser Faktor war bei allen Entitäten mit mindestens einem emotionalen Problem signifikant assoziiert. Weitere signifikante Assoziationen wurden für einen schlechteren Allgemeinzustand (maligne Gliome), weibliches Geschlecht (Lungenkarzinome, Kopf-Hals-Karzinome), jüngeres Alter (Lungenkarzinome) und Inoperabilität (gynäkologische Malignome) gefunden. Trends zeigten sich für ein fortgeschrittenes Tumorstadium (Prostatakarzinome, maligne Gliome), eine zusätzliche Chemotherapie (gynäkologische Malignome, Lungenkarzinome), weitere Malignome in der Eigenanamnese (gynäkologische Malignome, Kopf-Hals-Karzinome und Prostatakarzinome), eine alleinige perkutane Strahlentherapie ohne Brachytherapie (Prostatakarzinom), ≥2 betroffene Areale (maligne Gliome) sowie die Tumorlokalisation (Kopf-Hals-Karzinome).

Obwohl die Ergebnisse unserer Studie in Bezug auf Prävalenz und Identifizierung von Risikofaktoren für emotionalen Stress mit den Ergebnissen früherer Studien übereinstimmen oder gut erklärt werden können, ist der retrospektive Charakter der Daten, insbesondere das Risiko eines versteckten Selektionsbias, bei deren Interpretation zu berücksichtigen. Als erste Arbeit, die alle sechs emotionalen Probleme, die mit dem NCCN Distress-Thermometer erfasst werden, bei mehreren Tumorentitäten untersucht hat, ist die vorliegende Dissertation für die individuelle Betreuung von Tumorpatient*innen von Bedeutung. Sie kann dazu beitragen, Risikopatient*innen bei einzelnen Tumorentitäten zu identifizieren, die von einer frühzeitigen psychoonkologischen Unterstützung bereits vor Beginn der Strahlentherapie profitieren können. Darüber hinaus kann diese kumulative Dissertation als Basis für zukünftige prospektive Studien dienen, die emotionalen Stress vor, während und nach einer Strahlentherapie untersuchen.

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VI. Anhang

VI.1 Verzeichnis der Publikationen im Rahmen der kumulativen Dissertation

(1) **Al-Salool A**, Soror T, Yu NY, Idel C, Bruchhage KL, Hakim SG, Rades D. Emotional Distress in Head-and-neck Cancer Patients Scheduled for Chemoradiation or Radiotherapy Alone. Anticancer Res. 2023 May;43(5):2227-2233. doi: 10.21873/anticanres.16386. PMID: 37097669.

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Emotional Distress in Head-and-neck Cancer Patients Scheduled for Chemoradiation or Radiotherapy Alone

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Abstract. *Background/Aim: Radiotherapy for head-and-neck cancer is often associated with significant toxicities, which may cause emotional distress. We evaluated prevalence and risk factors for pre-treatment emotional problems in patients irradiated for head-and-neck cancer. Patients and Methods: Twelve characteristics were retrospectively investigated in 213 patients for associations with emotional problems (worry, fear, sadness, depression, nervousness, loss of interest). After Bonferroni adjustment, p-values <0.0042 were regarded significant. Results: At least one emotional problem was reported by 131 patients (61.5%). Specific prevalence for emotional problems ranged between 10% and 44%. Physical complaints showed significant associations with all six emotional problems (p<0.0001) and female sex with sadness (p=0.0013). Trends were found for associations between female sex and fear (p=0.0097), history of another tumor and sadness (p=0.043), worse performance status and nervousness (p=0.012), and cancer site (oropharynx/oral cavity) and nervousness (p=0.063). Conclusion: More than 60% of patients reported emotional distress prior to radiotherapy for head-and-neck cancer. Patients with risk factors likely require near-term psycho-oncological assistance.*

Radiotherapy with or without concurrent chemotherapy is a standard treatment for head-and-neck cancers and often associated with significant acute and late toxicities (1-9). Potential adverse events of radiotherapy include radiation dermatitis, oral mucositis, dysphagia, dysgeusia, hypothyroidism and xerostomia (1-6). Administration of concurrent chemotherapy increases radiation-related toxicities and adds chemotherapy-specific adverse events including nausea and vomiting, decreased renal function, hearing problems, polyneuropathy, and hematologic toxicity (7-11). When looking at the severity and number of potential treatment-related side effects, it becomes obvious that a considerable number of head-and-neck cancer patients assigned to radiotherapy or radio-chemotherapy experience significant emotional distress. When compared to radiotherapy of other tumor sites, head-and-neck cancer patients wear a tight mask over the head and shoulders which may cause further distress (12).

In the literature, the prevalence of depression and anxiety, both aspects of emotional distress, prior to radiotherapy for head-and-neck cancer ranged between 8% and 58% and between 20% and 40%, respectively (13-17). Given the lack of data and inconsistency, particularly with respect to depression, additional studies are needed to better define the prevalence of emotional distress in head-and-neck cancer patients assigned to radiotherapy. Moreover, other aspects of emotional distress included in the National Comprehensive Cancer Network (NCCN) Distress Thermometer, namely worry, fear, sadness, nervousness, and loss of interest in usual activities, should be considered (18). In this study, all aspects of emotional distress of the NCCN Distress Thermometer are separately evaluated with respect to prevalence and potential risk factors (18). The knowledge of risk factors will contribute to identification of head-and-neck cancer patients who may require near-term psycho-oncological assistance prior to their course of radiotherapy or radio-chemotherapy.

Patients and Methods

A total of 213 head-and-neck cancer patients recommended for loco-regional radiotherapy or radio-chemotherapy according to the decision of a multidisciplinary tumor board were included in this retrospective study, which was approved by the local Ethics Committee (University of Lübeck, 2022-412).

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Key Words: Head-and-neck cancer, radio-chemotherapy, radiotherapy alone, emotional distress.

Table I. *Associations of the investigated characteristics and worry.*

Characteristic		Worry, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=119)	50 (42)	69 (58)	0.094
	During (n=94)	29 (31)	65 (69)	
Number of physical complaints	≤4 (n=124)	25 (20)	99 (80)	**<0.0001**
	≥5 (n=89)	54 (61)	35 (39)	
Age	≤65 Years (n=117)	46 (39)	71 (61)	0.46
	≥66 Years (n=96)	33 (34)	63 (66)	
Sex	Female (n=52)	23 (44)	29 (56)	0.22
	Male (n=161)	56 (35)	105 (65)	
Karnofsky performance score	≤80 (n=91)	36 (40)	55 (60)	0.52
	≥90 (n=122)	43 (35)	79 (65)	
Main tumor site	Oropharynx/OC (n=129)	47 (36)	82 (64)	0.81
	Other sites (84)	32 (38)	52 (62)	
p16-status*	Negative (n=97)	33 (39)	52 (61)	0.70
	Positive (n=59)	24 (42)	33 (58)	
Upfront surgery	No (n=79)	31 (39)	48 (61)	0.62
	Yes (n=134)	48 (36)	86 (64)	
Primary tumor category	T1-T2 (n=79)	32 (41)	47 (59)	0.43
	T3-T4 (n=134)	47 (35)	87 (65)	
Nodal status	Negative (n=57)	18 (32)	39 (68)	0.31
	Positive (n=156)	61 (39)	95 (61)	
Scheduled for concurrent chemotherapy	No (n=68)	23 (34)	45 (66)	0.50
	Yes (n=145)	56 (39)	89 (61)	
History of another tumor	No (n=175)	63 (36)	112 (64)	0.48
	Yes (n=38)	16 (42)	22 (58)	

COVID-19: Coronavirus Disease 2019; OC: oral cavity; HPV: human papilloma virus. *Not available in 57 patients. After application of the Bonferroni correction, *p*-values <0.0042 are significant with an alpha level <0.05 (bold *p*-values).

Seventy-nine patients (37%) received definitive irradiation using volumetric modulated arc therapy (VMAT). The mean total dose was 70 Gy (5×2.0 Gy per week). Sixty-eight of these patients were scheduled for concurrent radio-chemotherapy with two courses of cisplatin (20 mg/m^2/d1-5 or 25 mg/m2/d1-4), administered every 4 weeks. Chemotherapy was finally refused by one patient and not given due to decrease of the performance status until the start of treatment in another patient. Cisplatin was administered as planned in 34 patients. Due to comorbidity, reduced performance status, treatment-related toxicity, or expected complications, 32 patients received alternative systemic therapies including carboplatin alone (n=18), cisplatin followed by carboplatin (n=8), mitomycin C with or without 5-fluorouracil (n=3), cetuximab (n=2), and paclitaxel (n=1). In four patients receiving definitive treatment, external-beam radiotherapy (EBRT) was supplemented by a brachytherapy boost.

A total of 134 patients received adjuvant radio-(chemo)therapy (VMAT). The mean total dose was 66 Gy (5×2.0 Gy per week). Extent of resection was microscopically complete (R0) in 99 patients (six patients with close margins), microscopically incomplete (R1) in 20 patients, macroscopically incomplete (R2) in three patients, and unclear in 12 patients. Seventy-seven patients with risk factors were scheduled for concurrent radio-chemotherapy with cisplatin. Chemotherapy was not given in one patient due to decreased performance status. Cisplatin was administered as planned in 57 patients (in two patients combined with pembrolizumab). Due to the reasons stated above, 19 patients received other systemic therapies, *i.e.*, carboplatin alone (n=17), cisplatin followed by carboplatin (n=1), or mitomycin C/5-fluorouracil (n=1). Four patients in an adjuvant situation were treated with brachytherapy alone (9-12 fractions of 3-4 Gy), and five patients received a brachytherapy boost in addition to EBRT.

In the entire cohort of 213 patients, we evaluated the prevalence of emotional distress, represented by six emotional problems (worry, fear, sadness, depression, nervousness, loss of interest in usual activities). These emotional problems were part of the NCCN Distress Thermometer completed by the patients prior to the informed consent discussion regarding their planned radio-(chemo)therapy (18).

In addition to evaluation of the prevalence, twelve characteristics were investigated for associations with each of the six emotional problems. These characteristics were timely connection to the COVID-19 pandemic (before *vs.* during), number of physical complaints (≤4 *vs.* ≥5), age (≤65 *vs.* ≥66 years, median=65 years), sex (female *vs.* male), Karnofsky performance score (KPS ≤80 *vs.* ≥90), main tumor site (oropharynx/oral cavity *vs.* other sites), p16-status as surrogate marker for the human papilloma virus (HPV)-status (negative *vs.* positive) (19), upfront surgery (no *vs.* yes), primary tumor category (T1-T2 *vs.* T3-T4), nodal status (negative *vs.* positive), being scheduled for concurrent chemotherapy (no *vs.* yes), and history of another tumor (no *vs.* yes).

Statistical analyses were performed with the Chi-square test or (if the number of patients was <5 in at least one subgroup) the Fisher's exact test. When using the Bonferroni adjustment to account for multiple comparisons, a *p*-value <0.0042 represented an alpha level of <0.05 and, therefore, was regarded as significant. Moreover, *p*-values <0.07 were regarded as representing a trend.

Table II. *Associations of the investigated characteristics and fear.*

Characteristic		Fear, n (%)		
		Yes	No	*p*-Value
COVID-19 pandemic	Before (n=119)	52 (44)	67 (56)	0.89
	During (n=94)	42 (45)	52 (55)	
Number of physical complaints	≤4 (n=124)	40 (32)	84 (68)	**<0.0001**
	≥5 (n=89)	54 (61)	35 (39)	
Age	≤65 Years (n=117)	57 (49)	60 (51)	0.14
	≥66 Years (n=96)	37 (39)	59 (61)	
Sex	Female (n=52)	31 (60)	21 (40)	0.0097
	Male (n=161)	63 (39)	98 (61)	
Karnofsky performance score	≤80 (n=91)	38 (42)	53 (58)	0.55
	≥90 (n=122)	56 (46)	66 (54)	
Main tumor site	Oropharynx/OC (n=129)	63 (49)	66 (51)	0.087
	Other sites (84)	31 (37)	53 (63)	
p16-status*	Negative (n=97)	38 (45)	47 (55)	0.60
	Positive (n=59)	28 (49)	29 (51)	
Upfront surgery	No (n=79)	36 (46)	43 (54)	0.75
	Yes (n=134)	58 (43)	76 (57)	
Primary tumor category	T1-T2 (n=79)	38 (48)	41 (52)	0.37
	T3-T4 (n=134)	56 (42)	78 (58)	
Nodal status	Negative (n=57)	23 (40)	34 (60)	0.50
	Positive (n=156)	71 (46)	85 (54)	
Scheduled for concurrent chemotherapy	No (n=68)	25 (37)	43 (63)	0.14
	Yes (n=145)	69 (48)	76 (52)	
History of another tumor	No (n=175)	75 (43)	100 (57)	0.42
	Yes (n=38)	19 (50)	19 (50)	

COVID-19: Coronavirus Disease 2019; OC: oral cavity; HPV: human papilloma virus. *Not available in 57 patients. After application of the Bonferroni correction, *p*-values <0.0042 are significant with an alpha level <0.05 (bold *p*-values).

Table III. *Associations of the investigated characteristics and sadness.*

Characteristic		Sadness, n (%)		
		Yes	No	*p*-Value
COVID-19 pandemic	Before (n=119)	36 (30)	83 (70)	0.56
	During (n=94)	25 (27)	69 (73)	
Number of physical complaints	≤4 (n=124)	18 (15)	106 (85)	**<0.0001**
	≥5 (n=89)	43 (48)	46 (52)	
Age	≤65 Years (n=117)	33 (28)	84 (72)	0.88
	≥66 Years (n=96)	28 (29)	68 (71)	
Sex	Female (n=52)	24 (46)	28 (54)	**0.0013**
	Male (n=161)	37 (23)	124 (77)	
Karnofsky performance score	≤80 (n=91)	28 (31)	63 (69)	0.55
	≥90 (n=122)	33 (27)	89 (73)	
Main tumor site	Oropharynx/OC (n=129)	41 (32)	88 (68)	0.21
	Other sites (84)	20 (24)	64 (76)	
p16-status*	Negative (n=97)	25 (29)	60 (71)	0.62
	Positive (n=59)	19 (33)	38 (67)	
Upfront surgery	No (n=79)	24 (30)	55 (70)	0.67
	Yes (n=134)	37 (28)	97 (72)	
Primary tumor category	T1-T2 (n=79)	27 (34)	52 (66)	0.17
	T3-T4 (n=134)	34 (25)	100 (75)	
Nodal status	Negative (n=57)	14 (25)	43 (75)	0.43
	Positive (n=156)	47 (30)	109 (70)	
Scheduled for concurrent chemotherapy	No (n=68)	18 (26)	50 (74)	0.63
	Yes (n=145)	43 (30)	102 (70)	
History of another tumor	No (n=175)	45 (26)	130 (74)	0.043
	Yes (n=38)	16 (42)	22 (58)	

COVID-19: Coronavirus Disease 2019; OC: oral cavity; HPV: human papilloma virus. *Not available in 57 patients. After application of the Bonferroni correction, *p*-values <0.0042 are significant with an alpha level <0.05 (bold *p*-values).

Table IV. *Associations of the investigated characteristics and depression.*

Characteristic		Depression, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=119)	12 (10)	107 (90)	0.90
	During (n=94)	9 (10)	85 (90)	
Number of physical complaints	≤4 (n=124)	2 (2)	122 (98)	**<0.0001**
	≥5 (n=89)	19 (21)	70 (79)	
Age	≤65 Years (n=117)	13 (11)	104 (89)	0.50
	≥66 Years (n=96)	8 (8)	88 (92)	
Sex	Female (n=52)	3 (6)	49 (94)	0.42
	Male (n=161)	18 (11)	143 (89)	
Karnofsky performance score	≤80 (n=91)	10 (11)	81 (89)	0.63
	≥90 (n=122)	11 (9)	111 (91)	
Main tumor site	Oropharynx/OC (n=129)	14 (11)	115 (89)	0.55
	Other sites (84)	7 (8)	77 (92)	
p16-status*	Negative (n=97)	9 (11)	76 (89)	0.54
	Positive (n=59)	8 (14)	49 (86)	
Upfront surgery	No (n=79)	11 (14)	68 (86)	0.13
	Yes (n=134)	10 (7)	124 (93)	
Primary tumor category	T1-T2 (n=79)	6 (8)	73 (92)	0.39
	T3-T4 (n=134)	15 (11)	119 (89)	
Nodal status	Negative (n=57)	2 (4)	55 (96)	0.071
	Positive (n=156)	19 (12)	137 (88)	
Scheduled for concurrent chemotherapy	No (n=68)	6 (9)	62 (91)	0.73
	Yes (n=145)	15 (10)	130 (90)	
History of another tumor	No (n=175)	16 (9)	159 (91)	0.45
	Yes (n=38)	5 (13)	33 (87)	

COVID-19: Coronavirus Disease 2019; OC: oral cavity; HPV: human papilloma virus. *Not available in 57 patients. After application of the Bonferroni correction, *p*-values <0.0042 are significant with an alpha level <0.05 (bold *p*-values).

Table V. *Associations of the investigated characteristics and nervousness.*

Characteristic		Nervousness, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=119)	40 (34)	79 (66)	0.67
	During (n=94)	29 (31)	65 (69)	
Number of physical complaints	≤4 (n=124)	27 (22)	97 (78)	**<0.0001**
	≥5 (n=89)	42 (47)	47 (53)	
Age	≤65 Years (n=117)	41 (35)	76 (65)	0.36
	≥66 Years (n=96)	28 (29)	68 (71)	
Sex	Female (n=52)	20 (38)	32 (62)	0.28
	Male (n=161)	49 (30)	112 (70)	
Karnofsky performance score	≤80 (n=91)	38 (42)	53 (58)	0.012
	≥90 (n=122)	31 (25)	91 (75)	
Main tumor site	Oropharynx/OC (n=129)	48 (37)	81 (63)	0.063
	Other sites (84)	21 (25)	63 (75)	
p16-status*	Negative (n=97)	24 (28)	61 (72)	0.39
	Positive (n=59)	20 (35)	37 (65)	
Upfront surgery	No (n=79)	24 (30)	55 (70)	0.63
	Yes (n=134)	45 (34)	89 (66)	
Primary tumor category	T1-T2 (n=79)	24 (30)	55 (70)	0.63
	T3-T4 (n=134)	45 (34)	89 (66)	
Nodal status	Negative (n=57)	17 (30)	40 (70)	0.63
	Positive (n=156)	52 (33)	104 (67)	
Scheduled for concurrent chemotherapy	No (n=68)	17 (25)	51 (75)	0.11
	Yes (n=145)	52 (36)	93 (64)	
History of another tumor	No (n=175)	57 (33)	118 (67)	0.91
	Yes (n=38)	12 (32)	26 (68)	

COVID-19: Coronavirus Disease 2019; OC: oral cavity; HPV: human papilloma virus. *Not available in 57 patients. After application of the Bonferroni correction, *p*-values <0.0042 are significant with an alpha level <0.05 (bold *p*-values).

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

Characteristic		Loss of interest in usual activities, n (%)		
		Yes	No	*p*-Value
COVID-19 pandemic	Before (n=119)	17 (14)	102 (86)	0.75
	During (n=94)	12 (13)	82 (87)	
Number of physical complaints	≤4 (n=124)	7 (6)	117 (94)	**<0.0001**
	≥5 (n=89)	22 (25)	67 (75)	
Age	≤65 Years (n=117)	14 (12)	103 (88)	0.44
	≥66 Years (n=96)	15 (16)	81 (84)	
Sex	Female (n=52)	5 (10)	47 (90)	0.33
	Male (n=161)	24 (15)	137 (85)	
Karnofsky performance score	≤80 (n=91)	13 (14)	78 (86)	0.81
	≥90 (n=122)	16 (13)	106 (87)	
Main tumor site	Oropharynx/OC (n=129)	19 (15)	110 (85)	0.56
	Other sites (84)	10 (12)	74 (88)	
p16-status*	Negative (n=97)	10 (12)	75 (88)	0.33
	Positive (n=59)	10 (18)	47 (82)	
Upfront surgery	No (n=79)	14 (18)	65 (82)	0.18
	Yes (n=134)	15 (11)	119 (89)	
Primary tumor category	T1-T2 (n=79)	12 (15)	67 (85)	0.61
	T3-T4 (n=134)	17 (13)	117 (87)	
Nodal status	Negative (n=57)	6 (11)	51 (89)	0.43
	Positive (n=156)	23 (15)	133 (85)	
Scheduled for concurrent chemotherapy	No (n=68)	9 (13)	59 (87)	0.91
	Yes (n=145)	20 (14)	125 (86)	
History of another tumor	No (n=175)	24 (14)	151 (86)	0.93
	Yes (n=38)	5 (13)	33 (87)	

COVID-19: Coronavirus Disease 2019; OC: oral cavity; HPV: human papilloma virus. *Not available in 57 patients. After application of the Bonferroni correction, *p*-values <0.0042 are significant with an alpha level <0.05 (bold *p*-values).

Results

At least one emotional problem was experienced by 131 patients (61.5%). The specific prevalence for the emotional problems, such as worry, fear, sadness, depression, nervousness, and loss of interest in usual activities was 37%, 44%, 29%, 10%, 32%, and 14%, respectively. A greater number of physical complaints showed significant associations with all six emotional problems ($p<0.0001$), and female sex was significantly associated with sadness ($p=0.0013$). A strong trend was found for an association between female sex and fear ($p=0.0097$). In addition, trends were observed for correlations between history of another tumor and sadness ($p=0.043$), a KPS ≤80 and nervousness ($p=0.012$), and between cancer site (oropharynx/oral cavity) and nervousness ($p=0.063$). The results of the complete analyses are presented in Table I, Table II, Table III, Table IV, Table V, and Table VI.

Discussion

Since radiotherapy and radio-chemotherapy of head-and-neck cancer often leads to burdensome side effects, patients assigned to one of these treatments may experience considerable emotional distress (1-9). In previous studies of head-and-neck cancer patients, 8-58% had depression and 20-40% of anxiety prior to radiation treatment (13-17). Moreover, in the study of Lewis *et al*., 56% of patients with head-and-neck cancer who were planned for cancer-directed radiotherapy had significant general (not further specified) distress (20). Furthermore, in our previous study, 44 of 103 (43%) head-and-neck cancer patients selected for definitive or adjuvant radio-(chemo)therapy reported sleep disorders that were significantly associated with the number of emotional problems ($p=0.001$) (21). In our present study, the proportion of patients who experienced at least one emotional problem was higher than the rates of depression, anxiety, and general distress found in previous studies (13-17, 20). However, the specific prevalence of the six investigated emotional problems in our study was within the range previously reported for depression and anxiety (13-17). This result demonstrates consistency of our data.

In addition to the prevalence of the six emotional problems, we aimed to identify corresponding risk factors. According to the results of this study, a higher number of physical complaints and female sex showed significant associations with at least one emotional problem. In addition, trends were found for history of another tumor, worse performance status, and

cancer site (oropharynx/oral cavity). The retrospective design of this study should be considered when interpreting its results. However, our findings are in line with those of previous studies. Neilson *et al*. found that higher depression and anxiety scores were related to the number of physical symptoms (15). In the study of Gosak *et al*., depression and anxiety were more frequently recorded by patients with nutritional problems and cachexia (14). Lewis *et al*. observed a tracheostomy tube, which likely led to physical complaints, to be predictive of general distress (20). In our previous study, sleep disorders were significantly correlated with more physical complaints (21). Moreover, in a study that investigated psychological distress over the course of radiotherapy in head-and-neck cancers and their caregivers, physical complaints, sleep problems, pain, sore mouth, eating problems, and fatigue were the most frequently stated causes of distress (22). In another study evaluating distress following radiotherapy, physical functioning was a significant predictor of anxiety (23). Associations between female sex and the incidence of depression and intensity of anxiety were found in the study of Wang *et al*. that investigated the psychological status of patients with nasopharynx cancer assigned to radiotherapy (13).

The impact of the history of another tumor on emotional distress was not previously described for head-and-neck cancer patients prior to radiotherapy. However, Ninu *et al*. found that distress was higher in patients with previous cancer in another area in their study investigating head-and-neck cancer patients during the first year following treatment (24). In addition, our previous study revealed an association between history of another malignancy and sleep disorders (p=0.012) (21). Moreover, fear of a recurrence of cancer was stated as major concern by patients with head-and-neck cancer in previous studies (25, 26). With respect to the prognostic impact of a worse performance score, an association between lower KPS and prevalence of sleep disorders was found in our previous study (21). In addition, Gunn *et al*. reported that a worse performance status was correlated with a higher symptom burden including distress prior to radiotherapy of head-and-neck cancer (27). Our finding that the tumor site may have an impact on the prevalence of emotional distress is supported by the study of Lewis *et al*. that demonstrated a significant correlation between cancer site (oral cavity) and general distress (p=0.02), and by our previous study that showed a trend for an association between cancer site (oropharynx) and sleep disorders (p=0.052) (20, 21). In contrast to the risk factors stated above, the COVID-19 pandemic was not associated with the prevalence of emotional distress. This result agrees with that of a previous cross-sectional study from Brazil that found no increase of distress levels during the pandemic in head-and-neck cancer undergoing radiotherapy (28).

In summary, more than 60% of patients reported emotional distress prior to radiotherapy for head-and-neck cancer. Patients with risk factors, *i.e*., greater number of physical complaints, female sex, history of another tumor, worse performance status, and cancer of the oropharynx or oral cavity, likely require near-term psycho-oncological assistance.

Conflicts of Interest

The Authors declare no conflicts of interest related 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 A. A.-S., D.R., and N.Y.Y. was reviewed and finally approved by all Authors.

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Prevalence of and Risk Factors for Emotional Distress in Patients Undergoing Radiotherapy for Lung Cancer

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Abstract. *Background/Aim: Quality of life of patients with lung cancer can be impaired by psychological distress. This study evaluated prevalence of and risk factors for emotional distress in patients undergoing radiotherapy or chemo-radiotherapy. Patients and Methods: Fourteen potential risk factors were retrospectively investigated in 144 patients. Emotional distress was evaluated with the National Comprehensive Cancer Network Distress Thermometer. Values of p<0.0036 (Bonferroni correction) were considered significant. Results: At least one emotional problem (worry, fear, sadness, depression, nervousness, loss of interest) was reported by the majority of patients (N=93, 65%). Prevalence of these problems was 37%, 38%, 31%, 15%, 32% and 23%, respectively. Physical problems were significantly associated with worry (p=0.0029), fear (p=0.0030), sadness (p<0.0001), depression (p=0.0008), nervousness (p<0.0001), and loss of interest (p<0.0001). Age ≤69 years was associated with worry (p=0.0003), and female sex with fear (p=0.0002) and sadness (p=0.0026). Trends were found for associations of age with sadness (p=0.045), female sex with nervousness (p=0.034), and chemoradiotherapy with worry (p=0.027). Conclusion: Many patients with lung cancer experience emotional distress. Early psycho-oncological assistance may be important, particularly for high-risk patients.*

Lung cancer is the second most common type of cancer worldwide with more than two million new cases per year (1). Many of these patients receive radiotherapy or chemoradiotherapy, either following surgery or as definitive treatment. The latter group mainly includes patients with small-cell lung cancer (SCLC) or unresectable non-small cell lung cancer (NSCLC) and patients not suitable for surgery due to poor performance score or advanced age. For patients with early-stage NSCLC who are not eligible for or do not wish surgical resection, stereotactic body radiation therapy (SBRT) is a standard of care (2).

Radiotherapy and chemoradiotherapy can be associated with significant acute and late toxicities, which may lead to emotional distress for patients recommended to receive one of these treatments (3-7). The prevalence of emotional distress, namely anxiety and depression, prior to radiotherapy for lung cancer ranges between 4% and 21% (8-10). In another study, anxiety (which generally includes worry and fear) and depression were reported by 53.6% and 65.5%, respectively, of those patients who received radiotherapy (11). Because of the inconsistency of the data in the literature, additional studies investigating the prevalence of emotional distress in patients with lung cancer are required. Moreover, the other aspects of emotional distress included in the National Comprehensive Cancer Network Distress Thermometer, *i.e.* sadness, nervousness, and loss of interest in usual activities, should be addressed (12). The current study evaluated the prevalence of all six aspects of emotional distress of the Distress Thermometer in a cohort of patients selected for radiotherapy or chemoradiotherapy for lung cancer (12). Moreover, it aimed to determine risk factors of emotional distress that will help identify patients who already need psycho-oncological assistance, prior to the start of their treatment.

Patients and Methods

In a cohort of 144 patients with lung cancer selected for radiotherapy or chemoradiotherapy between January 2018 and March 2022, the prevalence of the six aspects of emotional distress included in the National Comprehensive Cancer Network Distress Thermometer, *i.e.* worry, fear, sadness, depression, nervousness, and loss of interest in usual activities, were determined (12). Moreover, 14 potential risk factors were retrospectively investigated for associations with these

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Key Words: Lung cancer, radiotherapy, chemoradiotherapy, pre-treatment emotional distress.

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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=86)	37 (43)	49 (57)	0.060
	During (n=58)	16 (28)	42 (72)	
Number of physical problems	0-4 (n=75)	19 (25)	56 (75)	**0.0029**
	≥5 (n=69)	34 (49)	35 (51)	
Age	≤69 Years (n=75)	38 (51)	37 (49)	**0.0003**
	≥70 Years (n=69)	15 (22)	54 (78)	
Sex	Female (n=54)	25 (46)	29 (54)	0.067
	Male (n=90)	28 (31)	62 (69)	
Karnofsky performance score	≤80 (n=88)	31 (35)	57 (65)	0.62
	≥90 (n=56)	22 (39)	34 (61)	
T-Category	1-2 (n=63)	21 (33)	42 (67)	0.50
	3-4 (n=80)	31 (39)	49 (61)	
N-Category	0-1 (n=69)	22 (32)	47 (68)	0.25
	2-3 (n=73)	30 (41)	43 (59)	
Distant metastasis	No (n=125)	47 (38)	78 (62)	0.61
	Yes (n=19)	6 (32)	13 (68)	
Histology	NSCLC (n=100)	37 (37)	63 (63)	0.27
	SCLC (n=29)	14 (48)	15 (52)	
Surgery prior to RT	No (n=123)	46 (37)	77 (63)	0.72
	Yes (n=21)	7 (33)	14 (67)	
Chemoradiotherapy	No (n=85)	25 (29)	60 (71)	0.027
	Yes (n=59)	28 (47)	31 (53)	
SBRT	No (n=118)	46 (39)	72 (61)	0.25
	Yes (n=26)	7 (27)	19 (73)	
History of another malignancy	No (n=96)	36 (38)	60 (63)	0.81
	Yes (n=48)	17 (35)	31 (65)	
Family history of malignancy	No (n=72)	24 (33)	48 (67)	0.52
	Yes (n=70)	27 (39)	43 (61)	

COVID-19: Coronavirus Disease 2019; NSCLC: non-small cell lung cancer; RT: radiotherapy; SBRT: stereotactic body radiation therapy; SCLC: small-cell lung cancer. After Bonferroni correction, values of $p<0.0036$ were considered significant and are shown in bold.

aspects. These factors included Coronavirus Disease 2019 (prior to *vs*. during the COVID-19 pandemic), number of physical problems stated by the patients when completing the Distress Thermometer (0-4 *vs*. ≥5 problems), age at radiotherapy (≤69 *vs*. ≥70 years, median=69 years); sex (female *vs*. male); Karnofsky performance score (≤80 *vs*. ≥90), primary tumor category (T1-T2 *vs*. T3-T4); nodal category (N0-N1 *vs*. N2-N3), distant metastasis (no *vs*. yes), histology (NSCLC *vs*. SCLC), surgery prior to radiotherapy (no *vs*. yes); chemoradiotherapy (no *vs*. yes), SBRT (no *vs*. yes), patient's own history of another malignancy (no *vs*. yes), and family history of another malignancy (no *vs*. yes). The study received approval from the Ethics Committee (University of Lübeck, reference number 2022-412).

Of the 144 patients (entire cohort), 100 patients had NSCLC (48 squamous cell carcinomas, 47 adeno carcinomas, five not otherwise specified) and 29 patients SCLC. In 15 patients, the histological type was not available or not specified. Of the patients with NSCLC, 79 patients received definitive radiotherapy (n=39) or chemoradiotherapy (n=40), and 21 patients received adjuvant treatment (n=19 and n=2, respectively). Eighty-eight patients were treated with volumetric-modulated arc therapy (planned total doses of 60-70 Gy with 2 Gy per fraction) and 12 patients with fractionated SBRT (42 to 64 Gy with 3 to 8 Gy per fraction). In the 42 patients with NSCLC receiving concurrent chemotherapy, systemic treatment consisted of cisplatin/vinorelbine in 18 patients, cisplatin/pemetrexed in 13 patients, nab-paclitaxel or paclitaxel in six patients, carboplatin/paclitaxel in four patients, and vinorelbine in one patient.

Of the 29 patients with SCLC, 12 patients received definitive radiotherapy and 17 patients definitive chemoradiotherapy. Twenty-eight patients were treated with volumetric modulated arc therapy (planned total doses of 56-66 Gy with 2 Gy per fraction) and one patient with fractionated SBRT (7×8 Gy). Concurrent chemotherapy consisted of cisplatin/etoposide in 11 patients, carboplatin/etoposide in five patients, and weekly paclitaxel following four neoadjuvant courses of cisplatin/etoposide in one patient. The 15 patients with unspecified histology were treated with definitive radiotherapy alone. Thirteen patients received fractionated SBRT (44 to 64 Gy with 4 to 8 Gy per fraction), and two patients volumetric-modulated arc therapy (one patient died after 6 Gy; radiotherapy was discontinued in one patient after 50 Gy).

Statistical analyses were mainly performed with chi-square test. When one or more subgroups included fewer than five patients, Fisher's exact test was applied. To consider the phenomenon of multiple comparisons, the Bonferroni correction was appliedand a value of $p<0.0036$ was then regarded as significant (alpha level <0.05). In addition, $p<0.05$ was considered to indicate a trend.

Table II. *Associations of the investigated characteristics and fear.*

Characteristic		Fear, n (%)		
		Yes	No	*p*-Value
COVID-19 pandemic	Before (n=86)	33 (38)	53 (62)	0.96
	During (n=58)	22 (38)	36 (62)	
Number of physical problems	0-4 (n=75)	20 (27)	55 (73)	**0.0030**
	≥5 (n=69)	35 (51)	34 (49)	
Age	≤69 Years (n=75)	34 (45)	41 (55)	0.066
	≥70 Years (n=69)	21 (30)	48 (70)	
Sex	Female (n=54)	31 (57)	23 (43)	**0.0002**
	Male (n=90)	24 (27)	66 (73)	
Karnofsky performance score	≤80 (n=88)	34 (39)	54 (61)	0.89
	≥90 (n=56)	21 (38)	35 (63)	
T-Category	1-2 (n=63)	23 (37)	40 (63)	0.67
	3-4 (n=80)	32 (40)	48 (60)	
N-Category	0-1 (n=69)	27 (39)	42 (61)	0.79
	2-3 (n=73)	27 (37)	46 (63)	
Distant metastasis	No (n=125)	50 (40)	75 (60)	0.25
	Yes (n=19)	5 (26)	14 (74)	
Histology	NSCLC (n=100)	36 (36)	64 (64)	0.23
	SCLC (n=29)	14 (48)	15 (52)	
Surgery prior to RT	No (n=123)	48 (39)	75 (61)	0.62
	Yes (n=21)	7 (33)	14 (67)	
Chemoradiotherapy	No (n=85)	28 (33)	57 (67)	0.12
	Yes (n=59)	27 (46)	32 (54)	
SBRT	No (n=118)	44 (37)	74 (63)	0.63
	Yes (n=26)	11 (42)	15 (58)	
History of another malignancy	No (n=96)	38 (40)	58 (60)	0.63
	Yes (n=48)	17 (35)	31 (65)	
Family history of malignancy	No (n=72)	24 (33)	48 (67)	0.24
	Yes (n=70)	30 (43)	40 (57)	

COVID-19: Coronavirus Disease 2019; NSCLC: non-small cell lung cancer; RT: radiotherapy; SBRT: stereotactic body radiation therapy; SCLC: small-cell lung cancer. After Bonferroni correction, values of $p<0.0036$ were considered significant and are shown in bold.

Results

At least one of the six emotional problems worry, fear, sadness, depression, nervousness, and loss of interest was reported by 93 patients (65%) prior to the start of treatment. The prevalence rates of these problems were 37%, 38%, 31%, 15%, 32% and 23%, respectively. Five or more physical problems were significantly associated with worry ($p=0.0029$) (Table I), fear ($p=0.0030$) (Table II), sadness ($p<0.0001$) (Table III), depression ($p=0.0008$) (Table IV), nervousness ($p<0.0001$) (Table V), and loss of interest ($p<0.0001$) (Table VI). In addition, age ≤69 years was significantly associated with worry ($p=0.0003$) (Table I) and female sex with fear ($p=0.0002$) (Table II) and sadness ($p=0.0026$) (Table III). Moreover, trends were found for associations between age ≤69 years and sadness ($p=0.045$) (Table III), between female sex and nervousness ($p=0.034$) (Table V), and between chemoradiotherapy and worry ($p=0.027$) (Table I). The complete results of the six analyses regarding associations between investigated potential risk factors and emotional problems are shown in Table I, Table II, Table III, Table IV, Table V and Table VI.

Discussion

Radiotherapy and chemoradiotherapy of lung cancer may cause various acute and late toxicities (3-7). Therefore, being assigned to such a treatment regimen can lead to significant emotional distress for patients with lung cancer. In the literature, the prevalence of pre-treatment emotional distress in patients with lung cancer varies (8-10). In a randomized controlled trial by Falk *et al.* comparing immediate to delayed palliative radiotherapy with 2×8.5 Gy or 1×10 Gy in 230 patients with unresectable NSCLC, baseline anxiety rates were 12% for those who underwent immediate treatment and 11% for those who underwent delayed treatment, respectively (8). Borderline anxiety was reported by additional 24% and 16% of patients,

Table III. *Associations of the investigated characteristics and sadness.*

Characteristic		Sadness, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=86)	29 (34)	57 (66)	0.44
	During (n=58)	16 (28)	42 (72)	
Number of physical problems	0-4 (n=75)	12 (16)	63 (84)	**<0.0001**
	≥5 (n=69)	33 (48)	36 (52)	
Age	≤69 Years (n=75)	29 (39)	46 (61)	0.045
	≥70 Years (n=69)	16 (23)	53 (77)	
Sex	Female (n=54)	25 (46)	29 (54)	**0.0026**
	Male (n=90)	20 (22)	70 (78)	
Karnofsky performance score	≤80 (n=88)	28 (32)	60 (68)	0.85
	≥90 (n=56)	17 (30)	39 (70)	
T-Category	1-2 (n=63)	20 (32)	43 (68)	0.95
	3-4 (n=80)	25 (31)	55 (69)	
N-Category	0-1 (n=69)	21 (30)	48 (70)	0.89
	2-3 (n=73)	23 (32)	50 (68)	
Distant metastasis	No (n=125)	42 (34)	83 (66)	0.18
	Yes (n=19)	3 (16)	16 (84)	
Histology	NSCLC (n=100)	29 (29)	71 (71)	0.21
	SCLC (n=29)	12 (41)	17 (59)	
Surgery prior to RT	No (n=123)	41 (33)	82 (67)	0.31
	Yes (n=21)	4 (19)	17 (81)	
Chemoradiotherapy	No (n=85)	25 (29)	60 (71)	0.57
	Yes (n=59)	20 (34)	39 (66)	
SBRT	No (n=118)	37 (31)	81 (69)	0.95
	Yes (n=26)	8 (31)	18 (69)	
History of another malignancy	No (n=96)	29 (30)	67 (70)	0.70
	Yes (n=48)	16 (33)	32 (67)	
Family history of malignancy	No (n=72)	23 (32)	49 (68)	0.80
	Yes (n=70)	21 (30)	49 (70)	

COVID-19: Coronavirus Disease 2019; NSCLC: non-small cell lung cancer; RT: radiotherapy; SBRT: stereotactic body radiation therapy; SCLC: small-cell lung cancer. After Bonferroni correction, values of $p<0.0036$ were considered significant and are shown in bold.

respectively, resulting in total anxiety rates of 36% and 27%, respectively. In that trial, baseline depression rates were 4% and 8%, respectively (8). Borderline depression was reported by an additional 17% and 12% of patients, respectively, resulting in total depression rates of 21% and 20%, respectively. In another randomized trial of 509 patients that compared 2×8.5 Gy to 13×3 Gy for unresectable NSCLC, psychological distress was reported by 17.8% and 17.1% of patients, respectively, prior to radiotherapy (9). In a prospective observational cohort study of 191 patients, pre-radiotherapy rates of anxiety were 21% in younger patients (aged 43-65 years) and 12% in elderly patients (aged 75-89 years), respectively. Prevalence rates of depression were 21% and 21%, respectively (10). Moreover, in a cross-sectional study in China, anxiety and depression were reported by 53.5% and 65.5%, respectively, of patients who received radiotherapy (11). The great variety of rates of emotional distress demonstrate that additional studies are required to properly define the seriousness of this complication. Therefore, the present study was performed to investigate the prevalence of the six emotional problems addressed by the National Comprehensive Cancer Network Distress Thermometer in patients assigned to radiotherapy or chemoradiotherapy for lung cancer (12). The prevalence rates ranged between 15% and 38%. These rates were similar to the total rates of anxiety and depression in the randomized trial of Falk *et al.* (8) and in younger patients of the prospective observational study of Turner *et al.* (10) that ranged between 20% and 36%. Moreover, when comparing patients aged ≥70 years of our study to the elderly patients of the study of Turner *et al.*, the rates of emotional problems were also similar (7-21% *versus* 12-21%) (10). The prevalence of emotional problems in the trial of Macbeth *et al.* (9) was lower than in our study and the trial of Falk *et al.* (8). This can be explained by the fact that the trial of Macbeth *et al.* was limited to patients with a good performance status (9). Moreover, 65% of our patients reported at least one emotional problem. This

Table IV. *Associations of the investigated characteristics and depression.*

Characteristic		Depression, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=86)	15 (17)	71 (83)	0.38
	During (n=58)	7 (12)	51 (88)	
Number of physical problems	0-4 (n=75)	4 (5)	71 (95)	**0.0008**
	≥5 (n=69)	18 (28)	51 (74)	
Age	≤69 Years (n=75)	15 (20)	60 (80)	0.10
	≥70 Years (n=69)	7 (10)	62 (90)	
Sex	Female (n=54)	11 (20)	43 (80)	0.19
	Male (n=90)	11 (12)	79 (88)	
Karnofsky performance score	≤80 (n=88)	15 (17)	73 (83)	0.46
	≥90 (n=56)	7 (13)	49 (88)	
T-Category	1-2 (n=63)	11 (17)	52 (83)	0.54
	3-4 (n=80)	11 (14)	69 (86)	
N-Category	0-1 (n=69)	9 (13)	60 (87)	0.57
	2-3 (n=73)	12 (16)	61 (84)	
Distant metastasis	No (n=125)	22 (18)	103 (82)	0.079
	Yes (n=19)	0 (0)	19 (100)	
Histology	NSCLC (n=100)	16 (16)	84 (84)	>0.99
	SCLC (n=29)	4 (14)	25 (86)	
Surgery prior to RT	No (n=123)	19 (15)	104 (85)	>0.99
	Yes (n=21)	3 (14)	18 (86)	
Chemoradiotherapy	No (n=85)	16 (19)	69 (81)	0.16
	Yes (n=59)	6 (10)	53 (90)	
SBRT	No (n=118)	18 (15)	100 (85)	>0.99
	Yes (n=26)	4 (15)	22 (85)	
History of another malignancy	No (n=96)	13 (14)	83 (86)	0.41
	Yes (n=48)	9 (19)	39 (81)	
Family history of malignancy	No (n=72)	13 (18)	59 (82)	0.27
	Yes (n=70)	8 (11)	62 (89)	

COVID-19: Coronavirus Disease 2019; NSCLC: non-small cell lung cancer; RT: radiotherapy; SBRT: stereotactic body radiation therapy; SCLC: small-cell lung cancer. After Bonferroni correction, values of $p<0.0036$ were considered significant and are shown in bold.

frequency was similar to the rates of anxiety and depression observed in a previous cross-sectional study (11). The fact that the prevalence rates found in our study were similar to the findings of most previous studies indicate consistency of our results.

In addition to the prevalence of emotional distress, we investigated potential risk factors. According to our results, at least one emotional problem was significantly associated with a greater number of physical problems, younger age, and female sex. In addition, a trend was found for an association with concurrent chemoradiotherapy. The fact that physical problems and symptoms increase psychological distress in patients with lung cancer was previously described for different situations (13-16). Moreover, in our previous study, a greater number of physical problems was identified as a significant risk factor for sleep disorders that can be a consequence of emotional distress (17). Associations between emotional distress and younger age were also found in other studies. In the prospective observational study of Turner *et al*., younger patients reported more concerns, and the prevalence of anxiety was non-significantly higher (10). In the cross-sectional study of Yan *et al*., patients reporting anxiety and depression were significantly younger than patients without these problems (11). Moreover, in the study of Mazanec *et al*. that investigated predictors of psycho-social adjustment following radiotherapy in patients with lung, breast or prostate cancer, younger age was associated with poor adjustment (18). An impact of sex on emotional distress was also found in previous studies of patients with lung cancer. In the study of Yan *et al*., female patients were more likely to experience anxiety (51% *vs*. 40%, $p=0.060$) and depression (64% *vs*. 54%, $p=0.067$) (11). In a study of lung cancer survivors, women had almost two-fold odds of being distressed, and in a study of patients with SCLC, women tended to have higher distress scores, indicating higher levels of distress (13, 19). The trend for an association between emotional distress and concurrent chemotherapy can be

Table V. *Associations of the investigated characteristics and nervousness.*

Characteristic		Nervousness, n (%)		
		Yes	No	*p*-Value
COVID-19 pandemic	Before (n=86)	23 (27)	63 (73)	0.10
	During (n=58)	23 (40)	35 (60)	
Number of physical problems	0-4 (n=75)	13 (17)	62 (83)	**<0.0001**
	≥5 (n=69)	33 (48)	36 (52)	
Age	≤69 Years (n=75)	29 (39)	46 (61)	0.071
	≥70 Years (n=69)	17 (25)	52 (75)	
Sex	Female (n=54)	23 (43)	31 (57)	0.034
	Male (n=90)	23 (26)	67 (74)	
Karnofsky performance score	≤80 (n=88)	29 (33)	59 (67)	0.74
	≥90 (n=56)	17 (30)	39 (70)	
T-Category	1-2 (n=63)	22 (35)	41 (65)	0.53
	3-4 (n=80)	24 (30)	56 (70)	
N-Category	0-1 (n=69)	20 (29)	49 (71)	0.62
	2-3 (n=73)	24 (33)	49 (67)	
Distant metastasis	No (n=125)	42 (34)	83 (66)	0.43
	Yes (n=19)	4 (21)	15 (79)	
Histology	NSCLC (n=100)	29 (29)	71 (71)	0.11
	SCLC (n=29)	13 (45)	16 (55)	
Surgery prior to RT	No (n=123)	42 (34)	81 (66)	0.21
	Yes (n=21)	4 (19)	17 (81)	
Chemoradiotherapy	No (n=85)	23 (27)	62 (73)	0.13
	Yes (n=59)	23 (39)	36 (61)	
SBRT	No (n=118)	39 (33)	79 (67)	0.54
	Yes (n=26)	7 (27)	19 (73)	
History of another malignancy	No (n=96)	30 (31)	66 (69)	0.80
	Yes (n=48)	16 (33)	32 (67)	
Family history of malignancy	No (n=72)	25 (35)	47 (65)	0.55
	Yes (n=70)	21 (30)	49 (70)	

COVID-19: Coronavirus Disease 2019; NSCLC: non-small cell lung cancer; RT: radiotherapy; SBRT: stereotactic body radiation therapy; SCLC: small-cell lung cancer. After Bonferroni correction, values of $p<0.0036$ were considered significant and are shown in bold.

explained by the fact that the addition of chemotherapy to radiotherapy significantly increases treatment-related acute toxicities, which has been demonstrated in several studies (20-24). Although the results of our study with respect to prevalence and identification of risk factors for emotional distress are in line with the results of previous studies or can be well explained, the retrospective nature of the data, particularly the risk of a hidden selection bias, needs to be considered during their interpretation.

In summary, many patients assigned to radiotherapy or chemoradiotherapy for lung cancer experience emotional distress. For patients with risk factors such as greater number of physical problems, younger age, female sex and concurrent chemotherapy, psycho-oncological assistance is important, ideally prior to the start of treatment.

Conflicts of Interest

The Authors state declare no conflicts of interest related to this study.

Authors' Contributions

The study was designed by all Authors. Data collection was performed by A. A.-S. and D.R.; data analysis by D.R. The article, which was drafted by D.R. and N.Y.Y., was reviewed and finally approved by all Authors.

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

Characteristic		Loss of interest in usual activities, n (%)		
		Yes	No	*p*-Value
COVID-19 pandemic	Before (n=86)	20 (23)	66 (77)	0.91
	During (n=58)	13 (22)	45 (78)	
Number of physical problems	0-4 (n=75)	5 (7)	70 (93)	**<0.0001**
	≥5 (n=69)	28 (41)	41 (59)	
Age	≤69 Years (n=75)	19 (25)	56 (75)	0.47
	≥70 Years (n=69)	14 (20)	55 (80)	
Sex	Female (n=54)	13 (24)	41 (76)	0.80
	Male (n=90)	20 (22)	70 (78)	
Karnofsky performance score	≤80 (n=88)	22 (25)	66 (75)	0.46
	≥90 (n=56)	11 (20)	45 (80)	
T-Category	1-2 (n=63)	12 (19)	51 (81)	0.31
	3-4 (n=80)	21 (26)	59 (74)	
N-Category	0-1 (n=69)	18 (26)	51 (74)	0.43
	2-3 (n=73)	15 (21)	58 (79)	
Distant metastasis	No (n=125)	31 (25)	94 (75)	0.24
	Yes (n=19)	2 (11)	17 (89)	
Histology	NSCLC (n=100)	23 (23)	77 (77)	0.61
	SCLC (n=29)	8 (28)	21 (72)	
Surgery prior to RT	No (n=123)	30 (24)	93 (76)	0.41
	Yes (n=21)	3 (14)	18 (86)	
Chemoradiotherapy	No (n=85)	17 (20)	68 (80)	0.32
	Yes (n=59)	16 (27)	43 (73)	
SBRT	No (n=118)	28 (24)	90 (76)	0.62
	Yes (n=26)	5 (19)	21 (81)	
History of another malignancy	No (n=96)	22 (23)	74 (77)	>0.99
	Yes (n=48)	11 (23)	37 (77)	
Family history of malignancy	No (n=72)	20 (28)	52 (72)	0.082
	Yes (n=70)	11 (16)	59 (84)	

COVID-19: Coronavirus Disease 2019; NSCLC: non-small cell lung cancer; RT: radiotherapy; SBRT: stereotactic body radiation therapy; SCLC: small-cell lung cancer. After Bonferroni correction, values of $p<0.0036$ were considered significant and are shown in bold.

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Pre-treatment Emotional Distress in Patients Receiving Radiotherapy for Gynecologic Cancers

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Abstract. *Background/Aim: Patients with gynecologic cancers selected for external-beam radiotherapy or brachytherapy may experience emotional distress. We aimed to identify patients who may benefit from early psycho-oncological intervention. Patients and Methods: We investigated 10 potential risk factors of emotional distress in a retrospective series of 122 patients planned for radiotherapy of gynecologic cancers. Factors included COVID-19 pandemic, number of physical problems, age, performance status, tumor site/stage, surgery, chemotherapy, brachytherapy, and history of another tumor. p-Values <0.005 indicated significance, and p-values <0.06 trends. Results: Frequencies of worry, fear, sadness, depression, nervousness, and loss of interest were 41%, 57%, 39%, 16%, 38%, and 20%, respectively. Significant associations with at least one of these symptoms were found for ≥5 physical problems and no upfront surgery. Trends were observed for chemoradiotherapy, history of another tumor, worse performance status, and younger age. Conclusion: The prevalence of pre-radiotherapy emotional distress was remarkable in patients with gynecologic cancers. Patients with risk factors may benefit from immediate psycho-oncological assistance.*

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Key Words: Gynecologic cancers, radiation therapy, emotional distress, risk factors.

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A considerable number of patients with gynecologic cancers experience psychological and emotional distress (1-4). In an analysis of survey data from a cohort study, emotional problems such as fear, nervousness, sadness, and worry were reported by 30 to 50% of patients, respectively (3). The burden of emotional distress may be particularly present in patients assigned to or undergoing radiotherapy or chemoradiation due to patient concerns regarding exposure to radiation, dependence on high-tech machines, and radiotherapy-induced adverse events (5-11). In a study of 480 patients irradiated for cervical cancer, up to 69% of the patients reported worry as a significant emotional problem (4). For these patients, psycho-oncological assistance may be important for treatment completion and outcomes. Therefore, our study aimed to investigate risk factors of pre-treatment emotional distress in order to identify those who may benefit from early psycho-oncological support.

Patients and Methods

A total of 10 potential risk factors were evaluated for associations with the six symptoms of emotional distress included in the National Comprehensive Cancer Network Distress Thermometer (worry, fear, sadness, depression, nervousness, loss of interest in usual activities) (12). This retrospective study (Ethics Committee, University of Lübeck, Germany, number 2022-412) included 122 patients who were planned to receive external-beam radiotherapy (EBRT) and/or brachytherapy (BT) for gynecologic cancer, *i.e.*, uterine (n=62), cervical (n=46) or vaginal/vulvar (n=14) cancer. Investigated factors were COVID-19 pandemic (prior to *versus* after the start of the pandemic), number of physical problems (0-4 *versus* ≥5), age at radiotherapy (≤65 *versus* ≥66 years), Karnofsky performance score (KPS ≤80 *versus* ≥90), primary tumor site (cervix uteri *versus* uterus *versus* vagina/vulva), tumor stage according to the International Federation of Gynecology and Obstetrics (FIGO-stage I-II *versus* II-IV), surgery prior to radiotherapy (no *versus* yes), chemotherapy before and/or during radiotherapy (no *versus* yes), history of another malignant tumor (no *versus* yes), and family history of malignant tumors (no *versus* yes).

All but one of the 62 patients with uterine cancer received upfront surgery. Radiotherapy regimens included 4×5 Gy of BT alone (n=46), EBRT alone (n=5), or a combination of both

Table I. *Associations of the investigated characteristics and worry.*

Characteristic		Worry, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=69)	29 (42)	40 (58)	0.79
	During (n=53)	21 (40)	32 (60)	
Number of physical problems	0-4 (n=72)	18 (25)	54 (75)	**0.0002**
	≥5 (n=50)	32 (64)	18 (36)	
Age	≤65 Years (n=64)	28 (44)	36 (56)	0.51
	≥66 Years (n=58)	22 (42)	36 (62)	
Karnofsky performance score	≤80 (n=37)	18 (49)	19 (51)	0.26
	≥90 (n=85)	32 (38)	53 (62)	
Primary tumor site	Cervix uteri (n=46)	21 (46)	25 (54)	0.20
	Uterus (n=62)	21 (34)	41 (66)	
	Vagina/vulva (n=14)	8 (57)	6 (43)	
FIGO-stage	I-II (n=75)	32 (43)	43 (57)	0.63
	III-IV (n=47)	18 (38)	29 (62)	
Surgery prior to RT	No (n=20)	15 (75)	5 (25)	**0.0007**
	Yes (n=102)	35 (34)	67 (66)	
Chemotherapy before and/or during RT	No (n=69)	24 (35)	45 (65)	0.11
	Yes (n=53)	26 (49)	27 (51)	
Treatment volume of RT	Without LN (n=47)	18 (38)	29 (62)	0.63
	With LN (n=75)	32 (43)	43 (57)	
Brachytherapy	No (n=41)	19 (46)	22 (54)	0.39
	Yes (n=81)	31 (38)	50 (62)	
History of another malignant tumor	No (n=107)	41 (38)	66 (62)	0.11
	Yes (n=15)	9 (60)	6 (40)	
Family history of malignant tumors	No (n=62)	24 (39)	38 (61)	0.62
	Yes (n=58)	25 (43)	33 (57)	

COVID-19: Coronavirus Disease 2019; FIGO: International Federation of Gynecology and Obstetrics; RT: radiotherapy; LN: lymph nodes. After Bonferroni correction, *p*-values <0.0042 are significant and shown in bold.

techniques (n=11). The median EBRT dose was 50.4 Gy (5×1.8 Gy per week). One patient with uterine cancer received personalized concurrent chemotherapy with weekly carboplatin and paclitaxel. Of the 46 patients with cervical cancer, 33 patients received upfront surgery. Of this subgroup, 12 patients were treated with 50.4 Gy (5×1.8 Gy per week) of EBRT alone and 13 patients with 50.4 Gy of EBRT plus BT (2 to 5×5 Gy or 3×7 Gy). Of the 13 patients receiving definitive radiotherapy, 7 patients were treated with EBRT alone (median dose=59.4 Gy) and 6 patients with EBRT (median dose=50.4 Gy) plus BT (5×5 Gy, 4×6 Gy, or 3 to 4×7 Gy). Forty-two of the 46 patients with cervical cancer received concurrent chemotherapy with weekly cisplatin (n=34), weekly carboplatin (n=7), or two courses of mitomycin C (n=1). Upfront surgery was performed in 8 of the 14 patients with vaginal and/or vulvar cancer. Seven of these patients received postoperative EBRT alone (median dose=50.4 Gy), and one patient 50.4 Gy of EBRT plus 4×5 Gy of BT. Five of the six patients receiving definitive radiotherapy were treated with EBRT alone (median dose=50.4 Gy), and one patient with 45.0 Gy of EBRT plus 3×6 Gy of BT. Seven of the 14 patients with vaginal and/or vulvar cancer received concurrent chemotherapy with weekly cisplatin (n=3), weekly carboplatin (n=2), or two courses of mitomycin C and 5-fluorouracil (n=2).

Associations between the potential risk factors and the six symptoms of emotional distress according to the National Comprehensive Cancer Network Distress Thermometer (12) were evaluated with the Chi-square test (number of patients ≥5 in all cells) or the Fisher's exact test (number of patients <5 in at least one cell). The Bonferroni correction was used to account for multiple comparisons, and *p*-values <0.005 were considered significant (alpha level <0.05). Moreover, *p*-values <0.06 indicated trends for associations between a potential risk factor and a symptom of emotional distress.

Results

Frequencies of the six symptoms of emotional distress, *i.e.*, worry, fear, sadness, depression, nervousness, and loss of interest in usual activities were 41%, 57%, 39%, 16%, 38%, and 20%, respectively. A greater number (≥5) of physical problems was significantly associated with worry (p=0.0002), fear (p=0.0041), sadness (p<0.0001), depression (p=0.0001), nervousness (p=0.0020), and loss of interest in usual activities (p<0.0001). In addition, no upfront surgery was significantly associated with worry (p=0.0007). Trends were found for associations between no upfront surgery and fear (p=0.026), nervousness (p=0.024) and loss of interest in usual activities (p=0.012), between additional chemotherapy and fear (p=0.026), between history of

Table II. *Associations of the investigated characteristics and fear.*

Characteristic		Fear, n (%)		
		Yes	No	*p*-Value
COVID-19 pandemic	Before (n=69)	40 (58)	29 (42)	0.72
	During (n=53)	29 (55)	24 (45)	
Number of physical problems	0-4 (n=72)	33 (46)	39 (54)	**0.0041**
	≥5 (n=50)	36 (72)	14 (28)	
Age	≤65 Years (n=64)	39 (61)	25 (39)	0.31
	≥66 Years (n=58)	30 (52)	28 (48)	
Karnofsky performance score	≤80 (n=37)	21 (57)	16 (43)	0.98
	≥90 (n=85)	48 (56)	37 (44)	
Primary tumor site	Cervix uteri (n=46)	30 (65)	16 (35)	0.29
	Uterus (n=62)	31 (50)	31 (50)	
	Vagina/vulva (n=14)	8 (57)	6 (43)	
FIGO-stage	I-II (n=75)	42 (56)	33 (44)	0.88
	III-IV (n=47)	27 (57)	20 (43)	
Surgery prior to RT	No (n=20)	16 (80)	4 (20)	0.026
	Yes (n=102)	53 (52)	49 (48)	
Chemotherapy before and/or during RT	No (n=69)	33 (48)	36 (52)	0.026
	Yes (n=53)	36 (68)	17 (32)	
Treatment volume of RT	Without LN (n=47)	22 (47)	25 (53)	0.085
	With LN (n=75)	47 (63)	28 (37)	
Brachytherapy	No (n=41)	28 (68)	13 (32)	0.063
	Yes (n=81)	41 (51)	40 (49)	
History of another malignant tumor	No (n=107)	57 (53)	50 (47)	0.057
	Yes (n=15)	12 (80)	3 (20)	
Family history of malignant tumors	No (n=62)	40 (65)	22 (35)	0.048
	Yes (n=58)	27 (47)	31 (53)	

COVID-19: Coronavirus Disease 2019; FIGO: International Federation of Gynecology and Obstetrics; RT: radiotherapy; LN: lymph nodes. After Bonferroni correction, *p*-values <0.0042 are significant and shown in bold.

another malignant tumor and fear ($p=0.057$) or nervousness ($p=0.057$), between KPS ≤80 and sadness ($p=0.055$), and between age ≤65 years and nervousness ($p=0.028$). Full results with respect to associations between potential risk factors and symptoms of emotional distress are given in Table I, Table II, Table III, Table IV, Table V, and Table VI.

Discussion

Gynecologic cancers are the second most common group of female malignancies (13). Many of these patients are treated with EBRT, BT or a combination of both techniques. A recommendation for radiotherapy may lead to considerable emotional distress requiring psycho-oncological assistance. There is a lack of studies focusing on the prevalence and risk factors of emotional distress prior to a course of radiotherapy for gynecologic cancer. This study investigated both aspects in a cohort of 122 patients irradiated for uterine, cervical, vaginal, or vulvar cancer. Emotional distress was characterized by the six symptoms of emotional distress included in the National Comprehensive Cancer Network Distress Thermometer, namely worry, fear, sadness, depression, nervousness, and loss of interest in usual activities (12). The frequencies of these symptoms ranged between 16% and 57%, and were not much different from those of previous studies in patients with gynecologic cancers in general (20% to 50%) or patients with cervical cancer during a course of radiotherapy (23% to 69%) (3, 4). These findings demonstrate consistency of the results of the present study.

In this study, significant associations with at least one of the six symptoms of the National Comprehensive Cancer Network Distress Thermometer (12) were found for ≥5 physical problems and no upfront surgery. A positive correlation between physical problems and emotional distress has been previously observed in other studies of patients with gynecologic cancers (10, 14). In the study by Cull *et al.* of women with early stage cervical cancer, psychological distress was significantly associated with physical complaints ($p<0.001$) and functional outcome ($p<0.02$) (10). In the study of Hazewinkle *et al.*, better mental well-being was inversely correlated to the severity of urogenital and defecation symptoms (14). Moreover, in our previous study evaluating sleep disorders that can be a consequence of emotional distress, the prevalence of sleep

Table III. *Associations of the investigated characteristics and sadness.*

Characteristic		Sadness, n (%)		
		Yes	No	*p*-Value
COVID-19 pandemic	Before (n=69)	30 (43)	39 (57)	0.20
	During (n=53)	17 (32)	36 (68)	
Number of physical problems	0-4 (n=72)	15 (21)	57 (79)	**<0.0001**
	≥5 (n=50)	32 (64)	18 (36)	
Age	≤65 Years (n=64)	27 (42)	37 (58)	0.38
	≥66 Years (n=58)	20 (34)	38 (66)	
Karnofsky performance score	≤80 (n=37)	19 (51)	18 (49)	0.055
	≥90 (n=85)	28 (33)	57 (67)	
Primary tumor site	Cervix uteri (n=46)	12 (26)	34 (74)	0.061
	Uterus (n=62)	30 (48)	32 (52)	
	Vagina/vulva (n=14)	5 (36)	9 (64)	
FIGO-stage	I-II (n=75)	33 (44)	42 (56)	0.12
	III-IV (n=47)	14 (30)	33 (70)	
Surgery prior to RT	No (n=20)	11 (55)	9 (45)	0.098
	Yes (n=102)	36 (35)	66 (65)	
Chemotherapy before and/or during RT	No (n=69)	31 (45)	38 (55)	0.097
	Yes (n=53)	16 (30)	37 (70)	
Treatment volume of RT	Without LN (n=47)	24 (41)	23 (49)	0.024
	With LN (n=75)	23 (31)	52 (69)	
Brachytherapy	No (n=41)	15 (37)	26 (63)	0.75
	Yes (n=81)	32 (40)	49 (60)	
History of another malignant tumor	No (n=107)	39 (36)	68 (64)	0.21
	Yes (n=15)	8 (53)	7 (47)	
Family history of malignant tumors	No (n=62)	24 (39)	38 (61)	0.93
	Yes (n=58)	22 (38)	36 (62)	

COVID-19: Coronavirus Disease 2019; FIGO: International Federation of Gynecology and Obstetrics; RT: radiotherapy; LN: lymph nodes. After Bonferroni correction, *p*-values <0.0042 are significant and shown in bold.

Table IV. *Associations of the investigated characteristics and depression.*

Characteristic		Depression, n (%)		
		Yes	No	*p*-Value
COVID-19 pandemic	Before (n=69)	9 (13)	60 (87)	0.38
	During (n=53)	10 (19)	43 (81)	
Number of physical problems	0-4 (n=72)	3 (4)	69 (96)	**0.0001**
	≥5 (n=50)	16 (32)	34 (68)	
Age	≤65 Years (n=64)	10 (16)	54 (84)	0.99
	≥66 Years (n=58)	9 (16)	49 (84)	
Karnofsky performance score	≤80 (n=37)	8 (22)	29 (78)	0.22
	≥90 (n=85)	11 (13)	74 (87)	
Primary tumor site	Cervix uteri (n=46)	7 (15)	39 (85)	0.81
	Uterus (n=62)	9 (15)	53 (85)	
	Vagina/vulva (n=14)	3 (21)	11 (79)	
FIGO-stage	I-II (n=75)	12 (16)	63 (84)	0.87
	III-IV (n=47)	7 (15)	40 (85)	
Surgery prior to RT	No (n=20)	5 (25)	15 (75)	0.20
	Yes (n=102)	14 (14)	88 (85)	
Chemotherapy before and/or during RT	No (n=69)	8 (12)	61 (88)	0.17
	Yes (n=53)	11 (21)	42 (79)	
Treatment volume of RT	Without LN (n=47)	8 (17)	39 (83)	0.73
	With LN (n=75)	11 (15)	64 (85)	
Brachytherapy	No (n=41)	7 (17)	34 (83)	0.75
	Yes (n=81)	12 (15)	69 (85)	
History of another malignant tumor	No (n=107)	16 (15)	91 (85)	0.70
	Yes (n=15)	3 (20)	12 (80)	
Family history of malignant tumors	No (n=62)	9 (15)	53 (85)	0.88
	Yes (n=58)	9 (16)	49 (84)	

COVID-19: Coronavirus Disease 2019; FIGO: International Federation of Gynecology and Obstetrics; RT: radiotherapy; LN: lymph nodes. After Bonferroni correction, *p*-values <0.0042 are significant and shown in bold.

Table V. *Associations of the investigated characteristics and nervousness.*

Characteristic		Nervousness, n (%)		
		Yes	No	*p*-Value
COVID-19 pandemic	Before (n=69)	27 (39)	42 (61)	0.71
	During (n=53)	19 (36)	34 (64)	
Number of physical problems	0-4 (n=72)	19 (26)	53 (74)	**0.0020**
	≥5 (n=50)	27 (54)	23 (46)	
Age	≤65 Years (n=64)	30 (47)	34 (53)	0.028
	≥66 Years (n=58)	16 (28)	42 (72)	
Karnofsky performance score	≤80 (n=37)	17 (46)	20 (54)	0.22
	≥90 (n=85)	29 (34)	56 (66)	
Primary tumor site	Cervix uteri (n=46)	21 (46)	25 (54)	0.36
	Uterus (n=62)	20 (32)	42 (68)	
	Vagina/vulva (n=14)	5 (36)	9 (64)	
FIGO-stage	I-II (n=75)	26 (35)	49 (65)	0.38
	III-IV (n=47)	20 (43)	27 (57)	
Surgery prior to RT	No (n=20)	12 (60)	8 (40)	0.024
	Yes (n=102)	34 (33)	68 (67)	
Chemotherapy before and/or during RT	No (n=69)	24 (35)	45 (65)	0.45
	Yes (n=53)	22 (42)	31 (58)	
Treatment volume of RT	Without LN (n=47)	15 (32)	32 (68)	0.30
	With LN (n=75)	31 (41)	44 (59)	
Brachytherapy	No (n=41)	17 (41)	24 (59)	0.54
	Yes (n=81)	29 (36)	52 (64)	
History of another malignant tumor	No (n=107)	37 (35)	70 (65)	0.057
	Yes (n=15)	9 (60)	6 (40)	
Family history of malignant tumors	No (n=62)	27 (44)	35 (56)	0.11
	Yes (n=58)	17 (29)	41 (71)	

COVID-19: Coronavirus Disease 2019; FIGO: International Federation of Gynecology and Obstetrics; RT: radiotherapy; LN: lymph nodes. After Bonferroni correction, *p*-values <0.0042 are significant and shown in bold.

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

Characteristic		Loss of interest in usual activities, n (%)		
		Yes	No	*p*-Value
COVID-19 pandemic	Before (n=69)	15 (22)	54 (78)	0.51
	During (n=53)	9 (17)	44 (83)	
Number of physical problems	0-4 (n=72)	4 (6)	68 (94)	**<0.0001**
	≥5 (n=50)	20 (40)	30 (60)	
Age	≤65 Years (n=64)	16 (25)	48 (75)	0.12
	≥66 Years (n=58)	8 (14)	50 (86)	
Karnofsky performance score	≤80 (n=37)	10 (27)	27 (73)	0.18
	≥90 (n=85)	14 (16)	71 (84)	
Primary tumor site	Cervix uteri (n=46)	12 (26)	34 (74)	0.38
	Uterus (n=62)	10 (16)	52 (84)	
	Vagina/vulva (n=14)	2 (14)	12 (86)	
FIGO-stage	I-II (n=75)	13 (17)	62 (83)	0.41
	III-IV (n=47)	11 (23)	36 (77)	
Surgery prior to RT	No (n=20)	8 (40)	12 (60)	0.012
	Yes (n=102)	16 (16)	86 (84)	
Chemotherapy before and/or during RT	No (n=69)	11 (16)	58 (84)	0.24
	Yes (n=53)	13 (25)	40 (75)	
Treatment volume of RT	Without LN (n=47)	8 (17)	39 (83)	0.56
	With LN (n=75)	16 (21)	59 (79)	
Brachytherapy	No (n=41)	9 (22)	32 (78)	0.65
	Yes (n=81)	15 (19)	66 (81)	
History of another malignant tumor	No (n=107)	22 (21)	85 (79)	0.73
	Yes (n=15)	2 (13)	13 (87)	
Family history of malignant tumors	No (n=62)	14 (23)	48 (77)	0.33
	Yes (n=58)	9 (16)	49 (84)	

COVID-19: Coronavirus Disease 2019; FIGO: International Federation of Gynecology and Obstetrics; RT: radiotherapy; LN: lymph nodes. After Bonferroni correction, *p*-values <0.0042 are significant and shown in bold.

problems was significantly associated with a greater number (≥4) of physical problems ($p<0.0001$) (15). The result that no upfront surgery was associated with increased emotional distress can be explained by the facts that the majority of these patients had advanced disease and that non-resectability is often associated with a worse prognosis. In a previous study in cervical cancer survivors, fear of disease progression was one of the three greatest fears reported by the patients (16).

In addition, trends were observed for associations between emotional distress and additional chemotherapy, history of another tumor, worse performance status, or younger age. The trend regarding additional chemotherapy can be explained by the increased toxicity of chemoradiation when compared to radiotherapy alone that was found in previous studies, reviews and meta-analyses (17-24). For example, in the randomized trial of Teng *et al.* in patients with cervical cancer, rates of treatment-related toxicities were 37% in the chemoradiation group and 18% in the radiotherapy alone group, respectively ($p=0.02$) (17). In a more recent randomized trial of patients with endometrial cancer, adverse events grade ≥2 and grade ≥3 were significantly ($p<0.0001$) more common in patients treated with chemoradiation than in patients receiving radiotherapy alone (18). Moreover, neuropathy persisted significantly more often after chemoradiation (19, 20). Another tumor in a patient's history may increase the level of emotional distress, as previously reported in a study of breast cancer patients receiving adjuvant radiotherapy (25). Moreover, fear of disease progression often means significant distress for many patients (16). Associations between worse performance score and high levels of distress were previously found in a large retrospective study of patients with breast and gynecologic cancers (26). An inverse correlation between age and distress was also found in previous studies of patients with gynecologic cancers and breast cancer (11, 25-28).

In summary, a considerable proportion of patients with gynecologic cancers experience emotional distress prior to the start of radiotherapy. Patients with risk factors including ≥5 physical problems, unresectable tumors, additional chemotherapy, history of another tumor, worse performance status, and younger age likely benefit from immediate psycho-oncological assistance.

Conflicts of Interest

The Authors report 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, which was drafted by D.R. and N.Y.Y., was reviewed and approved by all Authors.

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Pre-treatment Emotional Distress in Patients Irradiated for Malignant Glioma

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Abstract. *Background/Aim: A recommendation of radiotherapy for patients with malignant gliomas may trigger emotional distress. Frequency and risk factors of this complication were investigated. Patients and Methods: Prevalence of six emotional problems and 11 potential risk factors were evaluated in 103 patients irradiated for grade II-IV gliomas. p-Values <0.0045 were considered significant. Results: Seventy-six patients (74%) had ≥1 emotional problem. Prevalence of specific emotional problems ranged between 23% and 63%. Associations were found between ≥5 physical problems and worry (p=0.0010), fear (p=0.0001), sadness (p=0.0023), depression (p=0.0006), and loss of interest (p=0.0006), and Karnofsky performance score ≤80 and depression (p=0.0002). Trends were found for physical problems and nervousness (p=0.040), age ≥60 years and depression (p=0.043) or loss of interest (p=0.045), grade IV glioma and sadness (p=0.042), and ≥2 involved sites and loss of interest (p=0.022). Conclusion: Three-fourths of glioma patients had pre-radiotherapy emotional distress. Psychological support should be offered very soon, particularly for high-risk patients.*

Diagnosis and treatment of malignant gliomas often lead to significant distress (1). Distress may be more pronounced if the patients are assigned to radiation therapy. Radiotherapy alone or in combination with chemotherapy is an integral part of the treatment for many glioma patients (2-5). Recommended radiation therapy may cause worry and fear regarding "unnecessary" radiation exposure, unknown technology, or potential adverse events (6-8). Patients may require early psycho-oncologic support to be able to sufficiently tolerate and complete the recommended treatment. In the literature, the prevalence of emotional or psychological distress varies considerably for patients with gliomas (6-61%) (1, 9-15). In our previous study, 67% of patients scheduled for radiotherapy of a malignant glioma reported sleep disorders prior to the start of their treatment, which may be correlated with emotional distress (16). However, there is little data focusing particularly on emotional distress prior to a course of radiotherapy or chemoradiation. Our study evaluates the frequency of six emotional problems and potential risk factors in patients with gliomas of WHO (World Health Organization) grades II, III, or IV, who were recommended for radiotherapy with or without chemotherapy.

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Key Words: Malignant glioma, glioblastoma multiforme, irradiation, emotional distress, risk factors.

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Patients and Methods

The data of 103 patients assigned to radiotherapy with or without chemotherapy for a WHO grade II-IV glioma between January 2018 and March 2022 were analyzed regarding emotional distress prior to their course of treatment (17, 18). Emotional distress was assessed according to the National Comprehensive Cancer Network (NCCN) Distress Thermometer and represented by six qualities including worry, fear, sadness, depression, nervousness, and loss of interest in usual activities (19). The study was approved by the local Ethics Committee at the University of Lübeck, Germany (identifier 2022-412).

The patients were irradiated using modern 3D treatment planning and volumetric-modulated arc therapy. Thirteen patients (12.6%) had a WHO grade II glioma, 10 patients (9.7%) a WHO grade III lesion, and 77 patients (74.8%) a WHO grade IV lesion (glioblastoma multiforme). In three patients (2.9%), the WHO grade was not specified. Of the 13 patients with a WHO grade II glioma,

11 patients received 54.0 Gy (5×1.8 Gy per week), and two patients 59.4 Gy (5×1.8 Gy per week). Eight patients were treated with upfront resection, and five patients received sequential (n=4) or concurrent (n=1) chemotherapy. Of the 10 patients with a WHO grade III glioma, four patients received 59.4 Gy (5×1.8 Gy per week), three patients 60.0 Gy (5×2.0 Gy per week), two patients 55.8 Gy (5×1.8 Gy per week), and one patient 30.4 of planned 59.4 Gy. Eight patients received upfront resection, and all patients chemoradiation, either sequential (n=9) or concurrent (n=1). Of the 77 patients with a WHO grade IV glioma, 58 patients (75%) were treated with 59.4 Gy (5×1.8 Gy per week), five patients with 60.0 Gy (5×2.0 Gy per week), five patients 55.8-57.6 Gy (5×1.8 Gy per week), and nine patients with other dose-fractionation regimens. Upfront resection was performed in 61 patients (79%), and chemoradiation with temozolomide in 70 patients (91%) (20).

Eleven potential risk factors of emotional distress were analyzed including Coronavirus Disease 2019 (COVID-19) pandemic (before *vs*. during the pandemic), number of physical problems (0-4 *vs*. ≥5), age (≤59 *vs*. ≥60 years), sex (female *vs*. male), Karnofsky performance score (KPS ≤80 *vs*. >80), number of cerebral sites involved by glioma (1 *vs*. ≥2 sites), WHO grade (II-III *vs*. IV), upfront resection (no *vs*. yes), chemoradiation (no *vs*. yes), treatment with dexamethasone corticosteroids at the time of assessment of pre-radiotherapy emotional distress (no *vs*. yes), and history of another malignancy (no *vs*. yes).

For statistical analyses, we used the Chi-square test or, if the number of patients was n<5 in one or more subgroups, the Fisher's exact test. Following the Bonferroni adjustment for multiple tests, a *p*-value <0.0045 was regarded significant (alpha level of <0.05). In addition, p<0.05 were considered to indicate a trend.

Results

Seventy-six patients (74%) showed at least one of the six investigated emotional problems. Prevalence of the emotional problems worry, fear, sadness, depression, nervousness, and loss of interest in usual activities was 53%, 63%, 49%, 21%, 40% and 23%, respectively. Significant associations were found between ≥5 physical problems and worry (p=0.0010), fear (p=0.0001), sadness (p=0.0023), depression (p=0.0006), and loss of interest in usual activities (p=0.0006), and between a KPS ≤80 and depression (p=0.0002). Moreover, trends were found for ≥5 physical problems and nervousness (p=0.040), age ≥60 years and depression (p=0.043) or loss of interest (p=0.045), grade IV glioma and sadness (p=0.042), and for ≥2 sites involved by glioma and loss of interest (p=0.022). All the results of the associations between the 11 potential risk factors and the six qualities of emotional distress are given in Table I, Table II, Table III, Table IV, Table V, and Table VI.

Discussion

Diagnosis and treatment of malignant brain tumors can lead to significant emotional and psychological distress. In the literature, emotional distress is often represented by anxiety and depression, or by the six qualities included in the NCCN Distress Thermometer, namely worry, fear, sadness, depression, nervousness, and loss of interest in usual activities (19). The prevalence of emotional distress shows considerable variations, depending on the patients' situation. In a prospective observational study of 149 patients with low-grade glioma, an increased level of distress was found in 20.8% of these patients (9). In a pilot study including 32 patients with high-grade glioma and 31 caregivers, 19 of the patients (60%) reported clinically significant distress (10). In another study considering both patients and caregivers, 37.5% of the patients with a primary brain tumor had distress scores above the cut-off value at the time of diagnoses (12). The study of Randazzo *et al*. used the NCCN Distress Thermometer to evaluate psychosocial distress in a series of 829 patients with a primary brain tumor (11, 19). The prevalence of worry, fear, and nervousness was 29.4%, 17.5%, and 22.4%, respectively. In the study of Mainio *et al*., 35% of the patients reported depression prior to resection of a primary brain tumor (15). Rooney *et al*. assessed five qualities of emotional distress using the Distress Thermometer at different time points (13). At the earliest time point, *i.e*., shortly after the start of radiotherapy or chemotherapy, worry, fear, sadness, depression, and nervousness were stated by 29%, 14%, 15%, 6%, and 19%, respectively. Moreover, in a systematic review that considered 92 articles, a prevalence of 60.9% was found for mental health disorders (1). No study so far focused specifically on the prevalence of emotional distress prior to radiotherapy or chemoradiation for malignant gliomas. In our study addressing this situation, 74% of the patients indicated at least one emotional problem. Moreover, the prevalence of the six investigated qualities of emotional distress was higher than that in the studies of Randazzo *et al*. and Rooney *et al*. (11, 13). These results support the hypothesis that upcoming radiotherapy is particularly stressful for glioma patients.

In our study, emotional distress was significantly associated with a greater number of physical problems and a lower KPS. In addition, trends were found for older age (≥60 years), glioblastoma multiforme, and involvement of ≥2 cerebral sites. The prognostic role of physical problems was previously described in other studies. In the study of Osoba *et al*., deteriorating neurologic status was associated with increase in emotional distress in patients with brain tumors (21). Halkett *et al*. found that poor physical function was related to multiple domains of distress in a cohort of 116 patients with high-grade gliomas (22). In the study of Aprile *et al*., mental aspects of quality of life were significantly related to fatigue, which is one of the physical problems addressed in the NCCN Distress Thermometer (19, 23). Moreover, in our preceding study, the number of physical problems were positively correlated with sleep disorders that might have been a consequence of emotional distress (13). Associations between a worse KPS and a higher prevalence

Table I. *Associations of the investigated characteristics and worry.*

Characteristic		Worry, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=59)	31 (53)	28 (47)	0.84
	During (n=44)	24 (55)	20 (45)	
Number of physical problems	0-4 (n=53)	20 (38)	33 (62)	**0.0010**
	≥5 (n=50)	35 (70)	15 (30)	
Age	≤59 Years (n=57)	32 (56)	25 (44)	0.53
	≥60 Years (n=46)	23 (50)	23 (50)	
Sex	Female (n=45)	25 (56)	20 (44)	0.70
	Male (n=58)	30 (52)	28 (48)	
Karnofsky performance score	≤80 (n=48)	27 (56)	21 (44)	0.59
	>80 (n=55)	28 (51)	27 (49)	
Number of involved sites	1 (n=71)	40 (56)	31 (44)	0.37
	≥2 (n=32)	15 (47)	17 (53)	
WHO grade*	II-III (n=23)	13 (57)	10 (43)	0.87
	IV (n=77)	42 (55)	35 (45)	
Upfront resection	No (n=25)	16 (64)	9 (36)	0.22
	Yes (n=78)	39 (50)	39 (50)	
Chemoradiation	No (n=18)	9 (50)	9 (50)	0.75
	Yes (n=85)	46 (54)	39 (46)	
Dexamethasone#	No (n=36)	18 (50)	18 (50)	0.66
	Yes (n=66)	36 (55)	30 (45)	
History of another malignancy#	No (n=84)	44 (52)	40 (48)	0.81
	Yes (n=18)	10 (56)	8 (44)	

COVID-19: Coronavirus Disease 2019; WHO: World Health Organization; *unknown in 3 patients; #unknown in 1 patient. Following Bonferroni adjustment, *p*-values <0.0045 are significant and given in bold.

Table II. *Associations of the investigated characteristics and fear.*

Characteristic		Fear, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=59)	36 (61)	23 (39)	0.61
	During (n=44)	29 (66)	15 (34)	
Number of physical problems	0-4 (n=53)	24 (45)	29 (55)	**0.0001**
	≥5 (n=50)	41 (82)	9 (18)	
Age	≤59 Years (n=57)	36 (63)	21 (37)	0.99
	≥60 Years (n=46)	29 (63)	17 (37)	
Sex	Female (n=45)	30 (67)	15 (33)	0.51
	Male (n=58)	35 (60)	23 (40)	
Karnofsky performance score	≤80 (n=48)	32 (67)	16 (33)	0.48
	>80 (n=55)	33 (60)	22 (40)	
Number of involved sites	1 (n=71)	43 (61)	28 (39)	0.43
	≥2 (n=32)	22 (69)	10 (31)	
WHO grade*	II-III (n=23)	14 (61)	9 (39)	0.72
	IV (n=77)	50 (65)	27 (35)	
Upfront resection	No (n=25)	19 (76)	6 (24)	0.12
	Yes (n=78)	46 (59)	32 (41)	
Chemoradiation	No (n=18)	12 (67)	6 (33)	0.73
	Yes (n=85)	53 (62)	32 (38)	
Dexamethasone#	No (n=36)	23 (64)	13 (36)	0.86
	Yes (n=66)	41 (62)	25 (38)	
History of another malignancy#	No (n=84)	53 (63)	31 (37)	0.87
	Yes (n=18)	11 (61)	7 (39)	

COVID-19: Coronavirus Disease 2019; WHO: World Health Organization; *unknown in 3 patients; #unknown in 1 patient. Following Bonferroni adjustment, *p*-values <0.0045 are significant and given in bold.

Table III. *Associations of the investigated characteristics and sadness.*

Characteristic		Sadness, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=59)	28 (47)	31 (53)	0.80
	During (n=44)	22 (50)	22 (50)	
Number of physical problems	0-4 (n=53)	18 (34)	35 (66)	**0.0023**
	≥5 (n=50)	32 (64)	18 (36)	
Age	≤59 Years (n=57)	27 (47)	30 (53)	0.79
	≥60 Years (n=46)	23 (50)	23 (50)	
Sex	Female (n=45)	20 (44)	25 (56)	0.46
	Male (n=58)	30 (52)	28 (48)	
Karnofsky performance score	≤80 (n=48)	28 (58)	20 (42)	0.063
	>80 (n=55)	22 (40)	33 (60)	
Number of involved sites	1 (n=71)	37 (52)	34 (48)	0.28
	≥2 (n=32)	13 (41)	19 (59)	
WHO grade*	II-III (n=23)	7 (30)	16 (70)	0.042
	IV (n=77)	42 (55)	35 (45)	
Upfront resection	No (n=25)	13 (52)	12 (48)	0.69
	Yes (n=78)	37 (47)	41 (53)	
Chemoradiation	No (n=18)	8 (44)	10 (56)	0.79
	Yes (n=85)	42 (49)	43 (51)	
Dexamethasone#	No (n=36)	15 (42)	21 (58)	0.34
	Yes (n=66)	34 (52)	32 (48)	
History of another malignancy#	No (n=84)	40 (48)	44 (52)	0.85
	Yes (n=18)	9 (50)	9 (50)	

COVID-19: Coronavirus Disease 2019; WHO: World Health Organization; *unknown in 3 patients; #unknown in 1 patient. Following Bonferroni adjustment, *p*-values <0.0045 are significant and given in bold.

Table IV. *Associations of the investigated characteristics and depression.*

Characteristic		Depression, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=59)	11 (19)	48 (81)	0.44
	During (n=44)	11 (25)	33 (75)	
Number of physical problems	0-4 (n=53)	4 (8)	49 (92)	**0.0006**
	≥5 (n=50)	18 (36)	32 (64)	
Age	≤59 Years (n=57)	8 (14)	49 (86)	0.043
	≥60 Years (n=46)	14 (30)	32 (70)	
Sex	Female (n=45)	12 (27)	33 (73)	0.25
	Male (n=58)	10 (17)	48 (83)	
Karnofsky performance score	≤80 (n=48)	18 (38)	30 (63)	**0.0002**
	>80 (n=55)	4 (7)	51 (93)	
Number of involved sites	1 (n=71)	16 (23)	55 (77)	0.66
	≥2 (n=32)	6 (19)	26 (81)	
WHO grade*	II-III (n=23)	5 (22)	18 (78)	0.92
	IV (n=77)	16 (21)	61 (79)	
Upfront resection	No (n=25)	7 (28)	18 (72)	0.35
	Yes (n=78)	15 (19)	63 (81)	
Chemoradiation	No (n=18)	2 (11)	16 (89)	0.35
	Yes (n=85)	20 (24)	65 (76)	
Dexamethasone#	No (n=36)	5 (14)	31 (86)	0.22
	Yes (n=66)	16 (24)	50 (76)	
History of another malignancy#	No (n=84)	18 (21)	66 (79)	0.76
	Yes (n=18)	3 (17)	15 (83)	

COVID-19: Coronavirus Disease 2019; WHO: World Health Organization; *unknown in 3 patients; #unknown in 1 patient. Following Bonferroni adjustment, *p*-values <0.0045 are significant and given in bold.

Table V. *Associations of the investigated characteristics and nervousness.*

Characteristic		Nervousness, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=59)	23 (39)	36 (61)	0.84
	During (n=44)	18 (41)	26 (59)	
Number of physical problems	0-4 (n=53)	16 (30)	37 (70)	0.040
	≥5 (n=50)	25 (50)	25 (50)	
Age	≤59 Years (n=57)	23 (40)	34 (60)	0.90
	≥60 Years (n=46)	18 (39)	28 (61)	
Sex	Female (n=45)	18 (40)	27 (60)	0.97
	Male (n=58)	23 (40)	35 (60)	
Karnofsky performance score	≤80 (n=48)	19 (40)	29 (60)	0.97
	>80 (n=55)	22 (40)	33 (60)	
Number of involved sites	1 (n=71)	27 (38)	44 (62)	0.58
	≥2 (n=32)	14 (44)	18 (56)	
WHO grade*	II-III (n=23)	9 (39)	14 (61)	0.99
	IV (n=77)	30 (39)	47 (61)	
Upfront resection	No (n=25)	11 (44)	14 (56)	0.62
	Yes (n=78)	30 (38)	48 (62)	
Chemoradiation	No (n=18)	9 (50)	9 (50)	0.33
	Yes (n=85)	32 (38)	53 (62)	
Dexamethasone#	No (n=36)	10 (28)	26 (72)	0.059
	Yes (n=66)	31 (47)	35 (53)	
History of another malignancy#	No (n=84)	33 (39)	51 (61)	0.69
	Yes (n=18)	8 (44)	10 (56)	

COVID-19: Coronavirus Disease 2019; WHO: World Health Organization; *unknown in 3 patients; #unknown in 1 patient. Following Bonferroni adjustment, *p*-values <0.0045 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=59)	12 (20)	47 (80)	0.41
	During (n=44)	12 (27)	32 (73)	
Number of physical problems	0-4 (n=53)	5 (9)	48 (91)	**0.0006**
	≥5 (n=50)	19 (38)	31 (62)	
Age	≤59 Years (n=57)	9 (16)	48 (84)	0.045
	≥60 Years (n=46)	15 (33)	31 (67)	
Sex	Female (n=45)	10 (22)	35 (78)	0.82
	Male (n=58)	14 (24)	44 (76)	
Karnofsky performance score	≤80 (n=48)	15 (31)	33 (69)	0.075
	>80 (n=55)	9 (16)	46 (84)	
Number of involved sites	1 (n=71)	12 (17)	59 (83)	0.022
	≥2 (n=32)	12 (38)	20 (63)	
WHO grade*	II-III (n=23)	5 (22)	18 (78)	0.87
	IV (n=77)	18 (23)	59 (77)	
Upfront resection	No (n=25)	7 (28)	18 (72)	0.52
	Yes (n=78)	17 (22)	61 (78)	
Chemoradiation	No (n=18)	4 (22)	14 (78)	>0.99
	Yes (n=85)	20 (24)	65 (76)	
Dexamethasone#	No (n=36)	5 (14)	31 (86)	0.090
	Yes (n=66)	19 (29)	47 (71)	
History of another malignancy#	No (n=84)	22 (26)	62 (74)	0.23
	Yes (n=18)	2 (11)	16 (89)	

COVID-19: Coronavirus Disease 2019; WHO: World Health Organization; *unknown in 3 patients; #unknown in 1 patient. Following Bonferroni adjustment, *p*-values <0.0045 are significant and given in bold.

of distress was previously reported by Mainio *et al.* (15). In addition, Rooney *et al.* found a significant association between KPS ≤70 and depressive disorders shortly after the start of radiotherapy for cerebral glioma (14). In the study of Abete-Fomara *et al.*, the probability to experience severe psychological distress was significantly associated with older age (odds ratio=1.17, p=0.0004) in patients with brain tumors (24). The fact that distress was correlated with more aggressive gliomas (higher WHO grades) was shown by Trad *et al.* (distress assessed at the time of diagnosis) and Leonetti *et al.* (distress assessed 6 months following resection) (12, 25). An association between emotional distress and involvement of ≥2 cerebral sites was not explicitly stated before. However, since this situation is associated with a significantly worse survival prognosis than a single lesion, one can understand that affected patients experience a higher level of distress (5).

In conclusion, approximately 75% of patients with a malignant glioma reported at least one aspect of emotional distress prior to their course of radiotherapy or chemoradiation. High-risk patients, namely those with ≥5 physical problems, KPS ≤80, age ≥60 years, glioblastoma multiforme, or involvement of ≥2 cerebral sites should be offered psychological support very soon.

Conflicts of Interest

The Authors report no conflicts of interest in relation to this study.

Authors' Contributions

All Authors participated in the study design. A. A.-L. and D.R. collected the data. Data analysis was performed by D.R. The article was drafted by D.R. and N.Y.Y.; it was reviewed and approved by all Authors.

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Prevalence and Risk Factors of Emotional Distress in Patients With Prostate Cancer Assigned to External-beam Radiotherapy With or Without High-dose Rate Brachytherapy

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Abstract. *Background/Aim: Upcoming radiotherapy for prostate cancer may lead to emotional distress. This study aimed to identify the prevalence and risk factors in a retrospective cohort of 102 patients. Patients and Methods: Thirteen characteristics were evaluated for six emotional problems. To account for multiple comparisons, Bonferroni correction was used; p-values <0.0038 were significant (alpha level <0.05). Results: Prevalence of worry, fears, sadness, depression, nervousness, and loss of interest in usual activities was 25%, 27%, 11%, 11%, 18%, and 5%, respectively. A greater number of physical problems was significantly associated with worry (p=0.0037) and fears (p<0.0001) and showed trends regarding sadness (p=0.011) and depression (p=0.011). Trends were also found for associations between younger age and worry (p=0.021), advanced primary tumor stage and fears (p=0.025), patient's history of another malignancy and nervousness (p=0.035), and between external-beam radiotherapy alone and fears (p=0.042) or nervousness (p=0.037). Conclusion: Although the prevalence of emotional distress was comparably low, patients with risk factors may benefit from early psychological support.*

Prostate cancer is the most common type of non-skin cancer among men in the United States and Europe, and the fourth most frequently diagnosed cancer worldwide (1). Many of these patients receive radiation therapy, either in the form of external-beam radiotherapy (EBRT) alone, brachytherapy alone, or a combination of both (2). In case of high risk or lymph node positive disease, radiotherapy often includes the elective pelvic lymph nodes. Prostate radiotherapy can be associated with significant acute and late toxicities and emotional distress (3-6). It is clinically relevant to identify patients who are at risk of experiencing emotional distress prior to or during prostate radiotherapy. These patients may benefit from early psychological support to guide them through the course of treatment. In this study, the prevalence of emotional distress and potential risk factors were evaluated in prostate cancer patients assigned to EBRT with or without a high-dose rate (HDR) brachytherapy boost.

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Key Words: Prostate cancer, radiotherapy, emotional problems, risk factors.

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Patients and Methods

One-hundred-and-two patients who received local or loco-regional radiotherapy for prostate cancer were retrospectively reviewed for six emotional problems including worry, fears, sadness, depression, nervousness, and loss of interest in usual activities (7). Each emotional problem was categorized as present or absent. The study achieved approval from the Ethics Committee at the University of Lübeck (2022-412). The patients had completed the National Comprehensive Cancer Network Distress Thermometer during the consent discussion regarding the planned radiotherapy (7).

Radiotherapy consisted of EBRT alone (n=76) or EBRT plus an HDR brachytherapy boost (n=26). Eleven of these 76 patients were scheduled for additional irradiation of loco-regional lymph nodes or pelvic lesions. Patients treated with EBRT alone were planned to receive total doses of 74-80 Gy (5×2 Gy per week) for definitive and 64-72 Gy (5×2 Gy per week) for adjuvant treatment, depending on tumor stage. Patients suitable for and agreeing to a brachytherapy boost were scheduled for 50 Gy of EBRT (5×2 Gy per week) plus two weekly fractions of 15 Gy of HDR brachytherapy. Prior EBRT, 50 patients had already received hormonal treatment, mainly with bicalutamide and/or leuprorelin-acetate.

For each of the six emotional problems stated above, 13 patient- and tumor-related characteristics were evaluated for potential associations. These characteristics included the relation to the COVID-19 pandemic (before *vs.* during), number of physical problems indicated by the patients when completing the distress thermometer (0-1 *vs.* ≥2), age at

Table I. *Associations of the investigated characteristics and worry.*

Characteristic		Worry, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=51)	16 (31)	35 (69)	0.11
	During (n=51)	9 (18)	42 (82)	
Number of physical problems	0-1 (n=46)	5 (11)	41 (89)	**0.0037**
	≥2 (n=56)	20 (36)	36 (64)	
Age	≤71 Years (n=53)	18 (34)	35 (66)	0.021
	≥72 Years (n=49)	7 (14)	42 (86)	
Karnofsky performance score	≤90 (n=40)	9 (23)	31 (78)	0.70
	100 (n=62)	16 (26)	46 (74)	
T-category*	1-2 (n=79)	19 (24)	60 (76)	0.76
	3-4 (n=22)	6 (27)	16 (73)	
Gleason-Score*	≤7 (n=57)	13 (23)	44 (77)	0.61
	8-9 (n=44)	12 (27)	32 (73)	
PSA level prior to RT**	<10 ng/ml (n=53)	12 (23)	41 (77)	0.60
	≥10 ng/ml (n=44)	12 (27)	32 (73)	
Surgery prior to RT	No (n=86)	21 (24)	65 (76)	>0.99*
	Yes (n=16)	4 (25)	12 (75)	
Hormone therapy prior to RT	No (n=52)	15 (29)	37 (71)	0.30
	Yes (n=50)	10 (20)	40 (80)	
Brachytherapy boost	No (n=76)	22 (29)	54 (71)	0.11
	Yes (n=26)	3 (12)	23 (88)	
Treatment volume of RT	Without LN (n=91)	22 (24)	69 (76)	>0.99
	With LN (n=11)	3 (27)	8 (73)	
History of another malignancy	No (n=89)	22 (25)	67 (75)	>0.99
	Yes (n=13)	3 (23)	10 (77)	
Family history of malignancy	No (n=52)	10 (19)	42 (81)	0.21
	Yes (n=50)	15 (30)	35 (70)	

COVID-19: Coronavirus Disease 2019; PSA: prostate-specific antigen; RT: radiotherapy; LN: lymph nodes; *unknown: n=1; **unknown: n=5. When applying Bonferroni correction, *p*-values <0.0038 are significant and shown in bold.

the start of EBRT (≤71 *vs.* ≥72 years, median=71 years), Karnofsky performance score (KPS ≤90 *vs.* 100), primary tumor stage represented by T-category (1-2 *vs.* 3-4), Gleason score (≤7 *vs.* 8-9), pre-radiotherapy prostate-specific antigen (PSA) level (<10 *vs.* ≥10 ng/ml), surgery (prostatectomy) prior to radiotherapy (no *vs.* yes), hormone therapy prior to radiotherapy (no *vs.* yes), brachytherapy boost in addition to EBRT (no *vs.* yes), treatment volume (without lymph nodes/pelvic lesions *vs.* with lymph nodes/pelvic lesions), patient's own history of another malignancy (no *vs.* yes), and family history of malignancy (no *vs.* yes).

Potential associations between these characteristics and the six emotional problems were analyzed using the Chi-square test or, if the number of patients in a subgroup was <5, the Fisher's exact test. Separate analyses were performed for each emotional problem. To account for multiple comparisons, the Bonferroni correction was used. *p*-Values <0.0038 were considered significant and represented an alpha level <0.05. In addition, *p*-values <0.05 were considered indicating a trend.

Results

The prevalence of the six emotional problems, namely worry, fears, sadness, depression, nervousness, and loss of interest in usual activities, was 25%, 27%, 11%, 11%, 18%, and 5%, respectively. A number of physical problems ≥2 was significantly associated with worry (p=0.0037) and fears (p<0.0001) and showed trends for associations with sadness (p=0.011) and depression (p=0.011). Moreover, trends were found for associations between age ≤71 years and worry (p=0.021), between tumor stage T3-4 and fears (p=0.025), between patient's own history of another malignancy and nervousness (p=0.035), and between EBRT alone (*i.e.*, without a brachytherapy boost) and fears (p=0.042) or nervousness (p=0.037). The complete results regarding the six emotional problems are summarized in Table I, Table II, Table III, Table IV, Table V, and Table VI.

Discussion

Radiotherapy of prostate cancer can be associated with significant genitourinary and gastro-intestinal toxicity. In patients scheduled for radiotherapy, the risk of experiencing such complications may lead to emotional distress, which can be assessed with the National Comprehensive Cancer Network Distress Thermometer (7). This instrument includes six emotional problems, namely worry, fears, sadness, depression,

Table II. *Associations of the investigated characteristics and fears.*

Characteristic		Fears, n (%)		
		Yes	No	*p*-Value
COVID-19 pandemic	Before (n=51)	11 (22)	40 (78)	0.18
	During (n=51)	17 (33)	34 (67)	
Number of physical problems	0-1 (n=46)	3 (7)	43 (93)	**<0.0001**
	≥2 (n=56)	25 (45)	31 (55)	
Age	≤71 Years (n=53)	18 (34)	35 (66)	0.13
	≥72 Years (n=49)	10 (20)	39 (80)	
Karnofsky performance score	≤90 (n=40)	11 (28)	29 (73)	0.99
	100 (n=62)	17 (27)	45 (73)	
T-category	1-2 (n=79)	17 (22)	62 (78)	0.025
	3-4 (n=22)	10 (45)	12 (55)	
Gleason-Score	≤7 (n=57)	16 (28)	41 (72)	0.73
	8-9 (n=44)	11 (25)	33 (75)	
PSA level prior to RT	<10 ng/ml (n=53)	18 (34)	35 (66)	0.14
	≥10 ng/ml (n=44)	9 (20)	35 (80)	
Surgery prior to RT	No (n=86)	21 (24)	65 (76)	0.11
	Yes (n=16)	7 (44)	9 (56)	
Hormone therapy prior to RT	No (n=52)	17 (33)	35 (67)	0.23
	Yes (n=50)	11 (22)	39 (78)	
Brachytherapy boost	No (n=76)	25 (33)	51 (67)	0.042
	Yes (n=26)	3 (12)	23 (88)	
Treatment volume of RT	Without LN (n=91)	23 (25)	68 (75)	0.16
	With LN (n=11)	5 (45)	6 (55)	
History of another malignancy	No (n=89)	23 (26)	66 (74)	0.34
	Yes (n=13)	5 (38)	8 (62)	
Family history of malignancy	No (n=52)	14 (27)	38 (73)	0.90
	Yes (n=50)	14 (28)	36 (72)	

COVID-19: Coronavirus Disease 2019; PSA: prostate-specific antigen; RT: radiotherapy; LN: lymph nodes. When applying Bonferroni correction, *p*-values <0.0038 are significant and shown in bold.

nervousness, and loss of interest in usual activities. In the present study, the prevalence of these problems ranged between 5% and 27%. These rates are similar to those found in other settings of patients with prostate cancer. In a retrospective study of 861 men who received EBRT, brachytherapy, or radical prostatectomy during the last seven years, the prevalence of anxiety and depression was 25% and 17%, respectively (8). In another study that investigated the value of the distress thermometer to predict global distress in prostate cancer patients, less than 20% of the patients reported scores of ≥4, the cut-off score for significant distress (9). Moreover, pre-treatment sleep disorders, which can be a consequence of emotional distress, were previously reported in 21% of patients assigned to local or loco-regional radiotherapy for prostate cancer (10). The prevalence of emotional distress in the present study was lower than that in a previous study of breast cancer patients, where frequencies ranged between 15% and 46% for the six emotional problems (11). These findings were supported by the study of Stapleton *et al.*, where the average distress of prostate cancer patients was significantly lower compared to breast cancer patients (12).

In our study, the prevalence of worry and fears was significantly associated with a greater number of physical problems including genitourinary and gastrointestinal disorders. In addition, the number of physical problems showed trends for associations with sadness and depression. These results are consistent with those of previous studies in other settings of prostate cancer. In a study using the data of 1,148 prostate cancer patients from a previous prospective study who had received surgery (63%) or radiation therapy (37%), patients with more impaired urinary, bowel, and sexual function reported greater emotional distress at different time points (13). In a study that analyzed the baseline data of a randomized trial including different treatments for prostate cancer, problems related to physical and daily living were significantly associated with global distress ($p<0.0005$) (9). In a prospective non-randomized study comparing different types of primary treatment for prostate cancer, psychological distress, depression, and anxiety were associated with urinary disorders and worsening of sexual function (14). Moreover, in a retrospective study of 253 patients treated with radical

Table III. *Associations of the investigated characteristics and sadness.*

Characteristic		Sadness, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=51)	5 (10)	46 (90)	0.75
	During (n=51)	6 (12)	45 (88)	
Number of physical problems	0-1 (n=46)	1 (2)	45 (98)	0.011
	≥2 (n=56)	10 (18)	46 (82)	
Age	≤71 Years (n=53)	7 (13)	46 (87)	0.53
	≥72 Years (n=49)	4 (8)	45 (92)	
Karnofsky performance score	≤90 (n=40)	6 (15)	34 (85)	0.27
	100 (n=62)	5 (8)	57 (92)	
T-category	1-2 (n=79)	9 (11)	70 (89)	>0.99
	3-4 (n=22)	2 (9)	20 (91)	
Gleason-Score	≤7 (n=57)	8 (14)	49 (86)	0.34
	8-9 (n=44)	3 (7)	41 (93)	
PSA level prior to RT	<10 ng/ml (n=53)	8 (15)	45 (85)	0.11
	≥10 ng/ml (n=44)	2 (5)	42 (95)	
Surgery prior to RT	No (n=86)	9 (10)	77 (90)	0.68
	Yes (n=16)	2 (13)	14 (88)	
Hormone therapy prior to RT	No (n=52)	6 (12)	46 (88)	0.80
	Yes (n=50)	5 (10)	45 (90)	
Brachytherapy boost	No (n=76)	11 (14)	65 (86)	0.061
	Yes (n=26)	0 (0)	26 (100)	
Treatment volume of RT	Without LN (n=91)	9 (10)	82 (90)	0.34
	With LN (n=11)	2 (18)	9 (82)	
History of another malignancy	No (n=89)	9 (10)	80 (90)	0.63
	Yes (n=13)	2 (15)	11 (85)	
Family history of malignancy	No (n=52)	7 (13)	45 (87)	0.53
	Yes (n=50)	4 (8)	46 (92)	

COVID-19: Coronavirus Disease 2019; PSA: prostate-specific antigen; RT: radiotherapy; LN: lymph nodes.

prostatectomy and 87 patients receiving EBRT for localized prostate cancer, patients tending to experience moderate to high distress had worse urinary or gastro-intestinal disorders (15). The results from previous studies were further supported by a review article considering 18 original and other review articles (16).

In addition to the impact of the number of physical problems on the development of emotional distress, the present study revealed trends for younger age, higher T-category, patient's history of another malignancy, and treatment with EBRT alone (without an HDR brachytherapy boost). Younger age was previously identified as risk factor for anxiety in long-term survivors after radical prostatectomy (17). Moreover, in the study of Lotfi-Jam *et al*. distressed patients were non-significantly younger than non-distressed patients (9). Mean age was 66.6 *vs*. 67.7 years (p=0.24), and 61.5% *vs*. 68.7% of the patients were 65 years or older (9). A higher T-category represents a more advanced tumor stage associated with a higher risk of a recurrence of prostate cancer. The fact that the fear of a recurrence is a significant burden for prostate cancer patients requiring psychosocial care has been described in several studies (18-20). Moreover, an advanced tumor stage requires higher doses of radiotherapy associated with an increased risk of acute and late toxicity, which likely results in higher levels of emotional distress. An association between advanced tumor stage and emotional distress prior to a course of radiotherapy was found also in a previous study of breast cancer patients (11). Similar to the fear of a recurrence, a history of another malignancy may contribute to the level of emotional distress. In the previous study of breast cancer patients, a trend was found between a positive own or family history of breast cancer or ductal carcinoma *in situ* and the prevalence of emotional problems (11). Another result of the present study was a trend between EBRT without an HDR brachytherapy boost and a higher prevalence of emotional problems. This finding may be explained by the fact that HDR brachytherapy is safe and associated with less toxicity than EBRT alone (3, 21). For example, in the study of Noda *et al*. no patient experienced grade ≥2 genitourinary toxicity, and no patient developed grade 3 late gastro-intestinal toxicity after EBRT plus an

Table IV. *Associations of the investigated characteristics and depression.*

Characteristic		Depression, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=51)	7 (14)	44 (86)	0.53
	During (n=51)	4 (8)	47 (92)	
Number of physical problems	0-1 (n=46)	1 (2)	45 (98)	0.011
	≥2 (n=56)	10 (18)	46 (82)	
Age	≤71 Years (n=53)	8 (15)	45 (85)	0.20
	≥72 Years (n=49)	3 (6)	46 (94)	
Karnofsky performance score	≤90 (n=40)	6 (15)	34 (85)	0.27
	100 (n=62)	5 (8)	57 (92)	
T-category	1-2 (n=79)	8 (10)	71 (90)	0.70
	3-4 (n=22)	3 (14)	19 (86)	
Gleason-Score	≤7 (n=57)	4 (7)	53 (93)	0.20
	8-9 (n=44)	7 (16)	37 (84)	
PSA level prior to RT	<10 ng/ml (n=53)	4 (8)	49 (92)	0.22
	≥10 ng/ml (n=44)	7 (16)	37 (84)	
Surgery prior to RT	No (n=86)	8 (9)	78 (91)	0.37
	Yes (n=16)	3 (19)	13 (81)	
Hormone therapy prior to RT	No (n=52)	5 (10)	47 (90)	0.70
	Yes (n=50)	6 (12)	44 (88)	
Brachytherapy boost	No (n=76)	11 (14)	65 (86)	0.061
	Yes (n=26)	0 (0)	26 (100)	
Treatment volume of RT	Without LN (n=91)	11 (12)	80 (88)	0.60
	With LN (n=11)	0 (0)	11 (100)	
History of another malignancy	No (n=89)	9 (10)	80 (90)	0.63
	Yes (n=13)	2 (15)	11 (85)	
Family history of malignancy	No (n=52)	4 (8)	48 (92)	0.35
	Yes (n=50)	7 (14)	43 (86)	

COVID-19: Coronavirus Disease 2019; PSA: prostate-specific antigen; RT: radiotherapy; LN: lymph nodes.

HDR brachytherapy boost (21). However, although the results of the present study agree with those of previous studies or, if novel, can be sufficiently explained, the retrospective design and the risk of a hidden selection bias need to be considered when interpreting the results.

In summary, the prevalence of six relevant emotional problems was determined, which was lower than that in previous studies of breast cancer patients. Despite the comparably low prevalence, a considerable number of prostate cancer patients have risk factors of emotional distress. In the present study, a greater number of physical problems, younger, advanced primary tumor stage, patient's history of another malignancy, and EBRT alone were identified as risk factors of emotional distress. Patients with these risk factors may benefit from early psychological support.

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

All Authors participated in the design of the study. A. A.-S. and D.R. provided the data that were analyzed by D.R. The article was drafted, reviewed and finally approved by all Authors.

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Table V. *Associations of the investigated characteristics and nervousness.*

Characteristic		Nervousness, n (%)		*p*-Value
		Yes	No	
COVID-19 pandemic	Before (n=51)	6 (12)	45 (88)	0.12
	During (n=51)	12 (24)	39 (76)	
Number of physical problems	0-1 (n=46)	5 (11)	41 (89)	0.10
	≥2 (n=56)	13 (23)	43 (77)	
Age	≤71 Years (n=53)	8 (15)	45 (85)	0.48
	≥72 Years (n=49)	10 (20)	39 (80)	
Karnofsky performance score	≤90 (n=40)	6 (15)	34 (85)	0.57
	100 (n=62)	12 (19)	50 (81)	
T-category	1-2 (n=79)	12 (15)	67 (85)	0.19
	3-4 (n=22)	6 (27)	16 (73)	
Gleason-Score	≤7 (n=57)	11 (19)	46 (81)	0.66
	8-9 (n=44)	7 (16)	37 (84)	
PSA level prior to RT	<10 ng/ml (n=53)	10 (19)	43 (81)	0.49
	≥10 ng/ml (n=44)	6 (14)	38 (86)	
Surgery prior to RT	No (n=86)	14 (16)	72 (84)	0.47
	Yes (n=16)	4 (25)	12 (75)	
Hormone therapy prior to RT	No (n=52)	9 (17)	43 (83)	0.93
	Yes (n=50)	9 (18)	41 (82)	
Brachytherapy boost	No (n=76)	17 (22)	59 (78)	0.037
	Yes (n=26)	1 (4)	25 (96)	
Treatment volume of RT	Without LN (n=91)	15 (16)	76 (84)	0.40
	With LN (n=11)	3 (27)	8 (73)	
History of another malignancy	No (n=89)	13 (15)	76 (85)	0.035
	Yes (n=13)	5 (38)	8 (62)	
Family history of malignancy	No (n=52)	9 (17)	43 (83)	0.68
	Yes (n=50)	9 (18)	41 (82)	

COVID-19: Coronavirus Disease 2019; PSA: prostate-specific antigen; RT: radiotherapy; LN: lymph nodes.

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

Characteristic		Loss of interest in usual activities, n (%)		
		Yes	No	*p*-Value
COVID-19 pandemic	Before (n=51)	3 (6)	48 (94)	>0.99
	During (n=51)	2 (4)	49 (96)	
Number of physical problems	0-1 (n=46)	0 (0)	46 (100)	0.062
	≥2 (n=56)	5 (9)	51 (91)	
Age	≤71 Years (n=53)	3 (6)	50 (94)	>0.99
	≥72 Years (n=49)	2 (4)	47 (96)	
Karnofsky performance score	≤90 (n=40)	4 (10)	36 (90)	0.076
	100 (n=62)	1 (2)	61 (98)	
T-category	1-2 (n=79)	3 (4)	76 (96)	0.30
	3-4 (n=22)	2 (9)	20 (91)	
Gleason-Score	≤7 (n=57)	2 (4)	55 (96)	0.65
	8-9 (n=44)	3 (7)	41 (93)	
PSA level prior to RT	<10 ng/ml (n=53)	3 (6)	50 (94)	>0.99
	≥10 ng/ml (n=44)	2 (5)	42 (95)	
Surgery prior to RT	No (n=86)	3 (3)	83 (97)	0.17
	Yes (n=16)	2 (13)	14 (88)	
Hormone therapy prior to RT	No (n=52)	2 (4)	50 (96)	0.68
	Yes (n=50)	3 (6)	47 (94)	
Brachytherapy boost	No (n=76)	5 (7)	71 (93)	0.33
	Yes (n=26)	0 (0)	26 (100)	
Treatment volume of RT	Without LN (n=91)	5 (5)	86 (95)	>0.99
	With LN (n=11)	0 (0)	11 (100)	
History of another malignancy	No (n=89)	3 (3)	86 (97)	0.12
	Yes (n=13)	2 (15)	11 (85)	
Family history of malignancy	No (n=52)	2 (4)	50 (96)	0.68
	Yes (n=50)	3 (6)	47 (94)	

COVID-19: Coronavirus Disease 2019; PSA: prostate-specific antigen; RT: radiotherapy; LN: lymph nodes.

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Emotional Distress Prior to Chemoradiation for Rectal or Anal Cancer

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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 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.

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Key Words: Rectal cancer, anal cancer, chemoradiation, emotional distress.

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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/m^2 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/m^2 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 ad 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/m^2 on day) and 5-FU (1,000 mg/m^2

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

Table II. *Associations of the investigated characteristics and fears.*

Characteristic		Fears, n (%)		
		Yes	No	*p*-Value
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 (%)		
		Yes	No	*p*-Value
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 (%)		
		Yes	No	*p*-Value
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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VI.2 Votum der Ethik-Kommission

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Aktenzeichen: 2022-412
16.06.2022 / IK

Verkürztes Verfahren - Anzeige
Antragsteller: Prof. Dr. med. Dirk Rades
Titel: Emotionaler Distress vor einer Strahlentherapie bei Patent*innen mit malignen Tumoren
Hier: Ihr Schreiben vom 15.06.2022

Sehr geehrter Herr Prof. Dr. med. Dirk Rades,

mit Ihrem o.g. Schreiben informieren Sie die Ethik-Kommission über Ihr geplantes Vorhaben. Die Ethik-Kommission nimmt das Vorhaben zustimmend zur Kenntnis.

Bitte reichen Sie zukünftig die Unterlagen nicht als Scan ein.

Mit freundlichen Grüßen

Prof. Dr. Alexander Katalinic
Vorsitzender der Ethik-Kommission

Allgemeine Hinweise:
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Seite 1 von 2

Vorgelegte Dokumente

1) 1187049294-265-18434-142-245.pdf vom 15.06.2022
2) Anschreiben.pdf vom 15.06.2022
3) Emotional Dsitress_solid tumors_Ethik_Basisformular.pdf vom 15.06.2022
4) nicht verfügbar - Studieninformation und Einwilligungserklärung.pdf vom 15.06.2022
5) nicht verfügbar - vertragliche Vereinbarungen.pdf vom 15.06.2022

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VI.4 Curriculum Vitae

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2005 - 2011	Studium für den Bachelor of Medicine, Bachelor of Surgery (MBBS) Sanaa Universität, Fakultät der Medizin und Gesundheitswissenschaft, Jemen

Vollständiges Publikationsverzeichnis

1. Rades D, Cacicedo J, Lomidze D, **Al-Salool A**, Segedin B, Groselj B, Jankarashvili N, Conde-Moreno AJ, Schild SE. A New and Easy-to-Use Survival Score for Patients Irradiated for Metastatic Epidural Spinal Cord Compression. Pract Radiat Oncol 2022;12:354-362. doi: 10.1016/j.prro.2022.03.012. PMID: 35395423.

2. Rades D, **Al-Salool A**, Staackmann C, Cremers F, Cacicedo J, Lomidze D, Segedin B, Groselj B, Jankarashvili N, Conde-Moreno AJ, Ciervide R, Kristiansen C, Schild SE. A New Clinical Instrument for Estimating the Ambulatory Status after Irradiation for Malignant Spinal Cord Compression. Cancers (Basel) 2022;14:3827. doi: 10.3390/cancers14153827. PMID: 35954490.

3. Rades D, Cacicedo J, Lomidze D, **Al-Salool A**, Segedin B, Groselj B, Schild SE. Prognostic Value of Preclinical Markers after Radiotherapy of Metastatic Spinal Cord Compression-An Additional Analysis of Patients from Two Prospective Trials. Cancers (Basel) 2022;14:2547. doi: 10.3390/cancers14102547. PMID: 35626151.

4. **Al-Salool A**, Soror T, Yu NY, Idel C, Bruchhage KL, Hakim SG, Rades D. Emotional Distress in Head-and-neck Cancer Patients Scheduled for Chemoradiation or Radiotherapy Alone. Anticancer Res 2023;43:2227-2233. doi: 10.21873/anticanres.16386. PMID: 37097669.

5. Rades D, **Al-Salool A**, Bohnet S, Yu NY. Prevalence of and Risk Factors for Emotional Distress in Patients Undergoing Radiotherapy for Lung Cancer. Anticancer Res 2023;43:2111-2118. doi: 10.21873/anticanres.16372. PMID: 37097662.

6. Rades D, **Al-Salool A**, Yu NY, Soror T. Pre-treatment Emotional Distress in Patients Receiving Radiotherapy for Gynecologic Cancers. Cancer Diagn Progn 2023;3:320-326. doi: 10.21873/cdp.10218. PMID: 37168969.

7. Rades D, **Al-Salool A**, Yu NY, Trillenberg P, Bonsanto MM, Leppert J. Pre-treatment Emotional Distress in Patients Irradiated for Malignant Glioma. In Vivo 2023;37:1198-1204. doi: 10.21873/invivo.13196. PMID: 37103101.

8. **Al-Salool A**, Soror T, Yu NY, Rades D. Prevalence and Risk Factors of Emotional Distress in Patients With Prostate Cancer Assigned to External-beam Radiotherapy With or Without High-dose Rate Brachytherapy. Anticancer Res 2023;43:2103-2109. doi: 10.21873/anticanres.16371. PMID: 37097699.

9. Rades D, **Al-Salool A**, Yu NY, Bartscht T. Emotional Distress Prior to Chemoradiation for Rectal or Anal Cancer. In Vivo 2023;37:1205-1210. doi: 10.21873/invivo.13197. PMID: 37103088.

Fortbildungen der allgemeinen beruflichen Weiterbildung

05.2022	28. Kongress der Deutschen Gesellschaft für Radioonkologie, Stuttgart
12.2021	Grundlagenkurs für Prüfer bei klinischen Prüfungen nach AMG einschließlich Hauptprüfer und Prüfer nach der VO (EU) 536/2014, ZKS Lübeck
09.2021	Spezialkurs im Strahlenschutz -Teletherapie und Brachytherapie-, Kiel
04.2021	Nasennebenhöhlenmalignome und Studienmanagement - IAG-KHT Frühjahrssymposium, online
11.2020	Kombinierter Kenntnis- und Grundkurs zum Erwerb der Fachkunde im Strahlenschutz für Ärzte gemäß StrlSchV, München
2017-2020	Über 100 Radioonkologische Tumorkonferenzen der besonderen Fälle, Göppingen
01.2020	30. Göppinger Tagung der Nieren- und Hochdruckerkrankungen und Dialyse, Göppingen
11.2019	Radioonkologie beim Lungenkarzinom heute & morgen, Stuttgart
10.2019	Treffpunkt Hepatologie: Radionuklid-Therapie und HVPG, Göppingen
10.2019	6. Ulmer Herbst Symposium, Ulm
06.2019	Highlights Amerikanischer Krebskongress 2019, Ulm
06.2019	Glioma 2019, Aktuelle Entwicklungen in der Hirntumortherapie Tübingen
04.2019	Neurologisches Symposium, Göppingen
11.2018	5. Ulmer Herbst Symposium Gyn-Update, Ulm
11.2017	2. Göppinger Hämatologische Fortbildung, Göppingen
11.2015 - 03.2016	Hospitation im Zentrum für Orthopädie und Unfallchirurgie Sankt Anna Hospital, Nordrhein-Westfalen
04 - 10.2015	Hospitation im Institut für Diagnostische und Interventionelle Radiologie, Uniklinikum Frankfurt, bei Prof. Vogl
01 - 04.2014	Hospitation in der Sonographie, Zentrum der Radiologie Al Askarie Krankenhaus, Sanaa, Jemen

Schulausbildung

2001-2004	High School “Allgemeinen Hochschulreife“, Sanaa
1998-2001	Middle School “weiterführende Schule“, Sanaa
1992-1998	Elementary School “Grundschule“, Sanaa