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Factors associated with cognitive impairment and cognitive concerns in patients with metastatic non-small cell lung cancer

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Abstract

Background. Knowledge regarding cognitive problems in metastatic non-small cell lung cancer (mNSCLC) is limited. Such problems may include both patient-reported cognitive concerns and demonstrable cognitive impairment. Greater understanding of these outcomes is needed to inform rehabilitation strategies for these difficulties. We aimed to identify the frequency of cognitive problems and associated factors in patients with mNSCLC.

Methods. In this cross-sectional study, adults with mNSCLC completed validated neuropsychological tests and self-report questionnaires measuring cognitive concerns, neurobehavioral concerns, depression, demoralization, illness intrusiveness, self-esteem, and physical symptoms. Cognitive impairment (performance based) was defined according to International Cancer and Cognition Task Force criteria. Clinically significant cognitive concerns were defined by a score ≥1.5 SD below the normative mean on the Functional Assessment of Cancer Therapy-Cognitive Function Perceived Cognitive Impairment (FACT-Cog PCI). Univariate and multivariate logistic regression analyses were performed to identify associated factors.

Results. Of 238 patients approached, 77 participated (median age: 62 years; range: 37-82). Brain metastases were present in 41 patients (53%), and 23 (29%) received cranial irradiation. Cognitive impairment and cognitive concerns were present in 31 (40%) and 20 patients (26%), respectively. Cognitive impairment and cognitive concerns co-occurred in 10 patients (13%), but their severity was unrelated. Cognitive impairment was associated with cranial irradiation (odds ratio [OR] = 2.89; $P = .04$), whereas cognitive concerns were associated with greater illness intrusiveness (OR = 1.04; $P = .03$) and lower self-esteem (OR = 0.86; $P = .03$).

Conclusions. Cognitive impairment and cognitive concerns are both common in patients with mNSCLC but are not necessarily related, and their risk factors differ. The association of illness intrusiveness and self-esteem with cognitive concerns can inform therapeutic interventions in this population.

Keywords

cancer-related cognitive impairment | lung cancer | neuro-oncology | neuropsychology | quality of life

Cognitive problems are common in patients with cancer, which include both patient-reported concerns about cognitive functioning and demonstrable cognitive impairment, and have received increasing attention in recent years.[1,2] Cognitive problems are multifactorial in origin and have been associated with patient and tumor characteristics, systemic and localized anti-tumor treatments, and psychological factors.[2] Current knowledge of cognitive problems in cancer patients is mainly based on research in brain and breast cancer patients.[1,2] However, they have also been reported in patients with other tumor types, including head and neck cancer,[3,4] hematological cancers,[5,6] and non-small cell lung cancer (NSCLC).[7]

More than 2.2 million people are diagnosed with lung cancer yearly worldwide,[8] most commonly with NSCLC,[9] in which the large majority develops metastatic disease.[10] However, studies examining cognitive problems in patients with metastatic NSCLC are scarce. Studies of cognitive impairment (ie, performance-based cognitive problems) in patients with NSCLC have mainly been conducted in the non-metastatic setting, reporting cognitive impairment rates of 30% to 71%.[11–15] Up to 50% of patients with mNSCLC eventually develop brain metastases,[16–18] and brain metastases and their associated treatment may additionally contribute to cognitive impairment. In that regard, the prevalence of cognitive impairment in unselected cancer patients with newly diagnosed brain metastases has been reported to range from 50% to 75%.[19–21] Cranial irradiation, particularly whole-brain radiotherapy (WBRT), has been associated with cognitive impairment in patients with brain metastases, including those with NSCLC brain metastases.[20,22–26] However, different systemic anti-tumor treatments may also contribute to cognitive impairment.[2]

The relationship between patient-reported cognitive concerns and cognitive impairment in patients with cancer is unclear. Some studies in brain and breast cancer patients showed little to no association between performance-based cognitive impairment and cognitive concerns.[27–29] Cognitive concerns are not only often related to psychological distress, including depressed mood and anxiety,[27–29] but may also reflect a patient's experience of the impact of cognitive problems on daily functioning, which is not necessarily captured by neuropsychological tests.[27] These differences underscore the need to measure both of these constructs when assessing cognitive problems. In patients with NSCLC, cognitive concerns have primarily been examined using self-report quality-of-life questionnaires.[7,30–33] Only one previous study systematically evaluated the presence of both cognitive impairment and cognitive concerns in patients with non-metastatic NSCLC. In that study, cognitive concerns were associated with depression and anxiety but not with impaired cognitive performance.[14]

The paucity of research on cognitive problems in patients with mNSCLC may partly be explained by the short survival associated with this disease, although newer targeted agents and immunotherapy have significantly improved survival in a subset of patients.[34] Information about the prevalence and determinants of both cognitive impairment and cognitive concerns in patients with mNSCLC, who now have longer survival times, is needed to develop appropriate rehabilitation approaches. Therefore, this study aimed to determine the frequency of cognitive impairment and cognitive concerns in patients with mNSCLC with and without brain metastases, and the factors associated with both types of cognitive problems.

Methods

Study Design and Population

This cross-sectional study included patients with mNSCLC who attended the lung cancer or brain metastases outpatient clinics of the Princess Margaret Cancer Centre in Toronto, Canada, between October 2018 and June 2019. Inclusion criteria were: age ≥ 18 years, diagnosis of mNSCLC, and fluency in English. Exclusion criteria were: the presence of primary brain tumors or psychiatric and neurological conditions that could interfere with the validity of the informed consent process or completion of study measures.

Study Procedure

All patients independently completed a neuropsychological test battery and questionnaires during a 1.5-hour session, scheduled before or after their routine clinic appointments. They were offered the opportunity to complete the questionnaires at home and were provided with a stamped, addressed envelope to return the questionnaires if they chose this option. Because emotional distress and cancer symptoms can impact cognitive problems, we also included validated self-reported questionnaires to assess emotional and physical distress. Demographics were obtained through structured interviews. Chart review was performed to extract disease and treatment-related variables, including date of mNSCLC diagnosis, disease characteristics (*EGFR* and *ALK* mutational status, presence and number of brain metastases), localized and systemic treatments received, and the presence of recent disease progression (defined as radiological progression or clinical deterioration within 1 month before the study visit). The Eastern Cooperative Oncology Group (ECOG) performance status within 15 days from the study visit was also extracted from the patient charts. Ethical approval was granted by the University Health Network Research Ethics Board (REB#18-5598), and written, informed consent was provided by all study patients.

Neuropsychological tests.—Cognitive impairment was assessed using standardized tests following the International Cognition and Cancer Task Force guidelines (ICCTF).[35]

Hopkins Verbal Learning Test-Revised (HVLT-R) measures verbal learning and memory. Test scores include total recall, as a measure of verbal learning (TR; number of words recalled after repeated learning trials), and delayed recall, as a measure of memory (DR; number of words recalled after a time delay).

Trail Making Test (TMT) consists of 2 parts: TMTA measures processing speed and visual attention, and TMTB measures executive functioning and mental flexibility. Scores are based on the time required to complete each part.

Controlled Oral Word Association (COWA) is a verbal fluency test, and the score is based on the number of words generated in response to phonemic cues within a minute.

Neuropsychological test scores were converted to *z*-scores based on published normative data, accounting for age, gender, and education (where appropriate). In accordance with ICCTF criteria,[35] patients were classified as having cognitive impairment if they had 2 or more test scores at least 1.5 SD below the normative mean or a single test score at least 2 SD below the mean. A cognitive composite (COG-comp) was constructed by averaging neuropsychological test *z*-scores (HVLT-R TR, HVLT-R DR, TMTA, TMTB, and COWA).

Self-report questionnaires.—*Functional Assessment of Cancer Therapy-Cognitive Function version 3* (FACT-Cog)[36] was used to assess the presence of cognitive concerns. This widely used and validated questionnaire consists of 37 statements related to cognitive problems, with respondents rating the frequency of those statements occurring in the past week on a 5-point Likert scale. We used the Perceived Cognitive Impairment subscale (FACT-Cog PCI) in our study, which includes 20 statements such as "I have had trouble forming thoughts" and "My thinking has been slow." Higher scores on the FACT-Cog PCI indicate fewer cognitive concerns. We transformed FACT-Cog PCI scores to *z*-scores based on normative data[37] from a healthy adult population. The presence of clinically significant cognitive concerns was defined as FACT-Cog PCI scores at least 1.5 SD below the normative mean.

Frontal Systems Behavior Scale (FrSBe)[38] is a validated questionnaire consisting of 46 items that assess neurobehavioral concerns. The items are scored on a 5-point Likert scale. Raw total FrSBe scores were converted to *T*-scores based on age, gender, and education. Higher scores indicate more neurobehavioral dysfunction, with *T*-scores of at least 65 being clinically significant.

Patient Health Questionnaire-9 (PHQ-9)[39] is a 9-item validated measure assessing depressive symptoms. The questionnaire is based on the *Diagnostic and Statistical Manual of Mental Disorders-IV* (DSM-IV) diagnostic criteria for major depression. The items are scored on a 4-point Likert scale, with scores of at least 10 representing the presence of at least moderate depression.

Demoralization Scale (DS)[40] is a 24-item, validated questionnaire assessing loss of meaning and purpose, dysphoria, disheartenment, helplessness, and a sense of failure. The items are scored on a 5-point Likert scale, and at least moderate demoralization was defined as scores of 30 or higher.

Illness Intrusiveness Rating Scale (IIRS)[41] is a validated measure assessing the illness-induced disruption of valued activities and interests, including work, recreation, and social relationships. The 13 items are scored on a 7-point Likert scale, with higher scores reflecting greater illness intrusiveness.

Rosenberg Self-Esteem Scale (RSE)[42] was used to evaluate an individual's global self-esteem, including positive and negative feelings about the self. The 10 items on this validated measure are scored on a 4-point Likert scale, and greater self-esteem is reflected by higher scores.

Memorial Symptom Assessment Scale-Short Form (MSAS-SF)[43] is a validated measurement that assesses the frequency and severity of 28 common physical symptoms in cancer patients scored on a 5-point Likert scale. Higher scores refer to a greater number and/or severity of symptoms.

When a patient skipped an item but completed at least half of the questionnaire items, scores were prorated (ie, the sum of the individual item scores was multiplied by the total number of scale items and subsequently divided by the number of items answered by the patient).[44]

Statistical Analysis

Statistical analyses were performed using SPSS Version 26.0 (IBM SPSS Statistics). For continuous variables, descriptive statistics were calculated, and for categorical variables, frequencies and percentages were presented. The relationship between cognitive impairment and cognitive concerns was evaluated using Pearson correlations.

Univariate binary logistic regression analyses were performed to identify factors associated with the presence of cognitive impairment or cognitive concerns. Variables included in the univariate analyses were sex, years of education, smoking history, disease variables (time since mNSCLC diagnosis, presence of a targetable mutation, disease progression, or brain metastases, and systemic or localized treatments received), psychological variables (neurobehavioral concerns, depression, demoralization, illness intrusiveness, and self-esteem), and physical symptoms. Time since mNSCLC diagnosis was converted into a binary variable using a median split (Table 1). In the analysis of cognitive impairment, the severity of cognitive concerns was also included as a predictor variable and vice versa for the analysis of cognitive concerns. Age was not included in the logistic regression analysis due to lack of variation within the study population. Variables that were significant at a *P*-value of ≤.10 in the univariate analyses were included in the corresponding multivariate binary logistic regression analyses of factors associated with the presence of cognitive impairment or cognitive concerns. The multivariate logistic regression analyses employed a backward likelihood method. Assumptions for the univariate and multivariate logistic regressions were tested prior to analyses. The presence of multicollinearity was examined using tolerance (<0.10) and Variance Inflation Factor > 10. The Box-Tidwell procedure was used to assess the linearity of the logit.[45]

Results

Of 238 eligible patients approached, study measures were completed by 78 patients (32%). One patient was excluded from analyses because of questionable English proficiency. Reasons for nonparticipation included lack of interest (n = 125), high symptom burden (n = 9), and the study being too time-consuming (n = 26). In total, 11 separate questionnaires and 1 COG-comp were missing,

Table 1. Demographic, Disease, and Treatment Characteristics of Study Patients

Variable	N (%) N = 77
Median age (range)[a]	62 (37-82)
Female	38 (49%)
Education; years median (range)	15 (4-25)
Native English-speaking[b]	66 (86%)
Median time since metastatic NSCLC diagnosis; months (range)	10 (0-89)
ECOG status	
0	23 (30%)
1	44 (57%)
2	8 (10%)
Missing	2 (3%)
Smoking history	53 (69%)
EGFR mutated	24 (31%)
ALK mutated	11 (14%)
Number of brain metastases	
0	36 (47%)
1-3	20 (26%)
≥ 4	21 (27%)
Disease progression	26 (34%)
Cranial progression	10 (13%)
Extra-cranial progression	4 (5%)
Both	12 (16%)
Cranial irradiation	23 (30%)
SRT	13 (17%)
WBRT	7 (9%)
SRT and WBRT	3 (4%)
Time since the first course of cranial irradiation; months median (range)[c]	11 (2-59)
Number of lines systemic treatment	
0	10 (13%)
1	28 (36%)
2	28 (36%)
≥3	11 (14%)
Active systemic treatment[a]	60 (78%)
Targeted therapies	29 (38%)
Immunotherapy	20 (26%)
Chemotherapy	11 (14%)
Received systemic treatment[d]	
Targeted therapies	31 (42%)
Immunotherapy	29 (38%)
Chemotherapy	37 (48%)
None	10 (13%)

Abbreviations: NSCLC, non-small cell lung cancer; SRT, stereotactic radiotherapy; WBRT, whole-brain radiotherapy.
[a]At the time of study visit.
[b]Including patients with ≥4 years of education in English.
[c]Eight patients had multiple courses of cranial irradiation; in those patients, the time since the last course of radiotherapy was 7 months (median, range: 0-23 months).
[d]Patients could have received multiple systemic treatments, including current treatment line.

and 9 other questionnaire scores were prorated[44] due to missing items.

Demographics and Clinical Characteristics

The median age of the 77 included patients was 62 years (range: 37-82 years), 32 patients (42%) were 60-70 years old, and 38 patients were female (49%; Table 1). Median time since mNSCLC diagnosis was 10 months (range: 0-89 months). Most patients' ECOG performance status was 0 or 1 (n = 67, 87%). *EGFR* and *ALK* mutations were present in 24 (31%) and 11 patients (14%), respectively. Recently detected disease progression was present in 26 patients (34%). Furthermore, 41 patients (53%) had brain metastases, and 23 of them (56%) received cranial radiotherapy (13 stereotactic radiotherapy [SRT], 7 WBRT, and 3 SRT and WBRT). The median time between the first course of cranial irradiation and study visit was 11 months (range: 2-59 months). Sixty patients (78%) were receiving active systemic treatment at time of study visit, which mainly consisted of targeted therapy (n = 29, 38%) and immunotherapy (n = 20, 26%).

Prevalence and Severity of Cognitive Problems

Clinically significant cognitive concerns were reported by 20 patients (26%), and cognitive impairment was observed in 31 patients (40%, Table 2). Of the patients with cognitive concerns, 10 patients (50%) did not meet the

Table 2. Cognitive Functioning Outcomes

Cognitive Functioning	Mean	Range	Impaired N (%)
Cognitive impairment			31 (40%)[a]
HVLT-R TR (*z*-score)	−0.73	(−3.1 to 1.5)	21 (27%)
HVLT-R DR (*z*-score)	−0.57	(−3.0 to 1.3)	18 (23%)
TMTA (*z*-score)	−0.002	(−4.5 to 1.9)	10 (13%)
TMTB (*z*-score)	−0.39	(−8.9 to 2.7)	15 (20%)
COWA (*z*-score)	−0.21	(−2.2 to 2.3)	12 (16%)
COG-comp	−0.38	(−2.7 to 1.6)	
	Median	Range	Impaired N (%)
Cognitive concerns (FACT-Cog PCI scores)	63	(27 to 80)	20 (26%)[b]

Abbreviations: COG-comp, cognitive composite; COWA, Controlled Oral Word Association; FACT-Cog PCI, Functional Assessment of Cancer Therapy-Cognitive Function Perceived Cognitive Impairment; HVLT-R DR, Hopkins Verbal Learning Test-Revised delayed recall; HVLT-R TR, Hopkins Verbal Learning Test-Revised total recall; TMTA, Trail Making Test (measures processing speed and visual attention); TMTB, Trail Making Test (measures executive functioning and mental flexibility).
[a]≥1.5 SD below the normative mean on ≥2 neuropsychological tests or ≥2 SD below the mean on a single test.
[b]FACT-Cog PCI scores of ≥1.5 SD below the normative mean.

criteria for cognitive impairment. The median FACT-Cog PCI score was 63 (range: 27-80). The mean COG-comp was –0.38 (SD = 0.86; range: –2.7 to 1.6), and the cognitive domains most often affected were verbal learning (HVLT-R TR, n = 21, 27%), memory (HVLT-R DR, n = 18, 23%), and executive functioning (TMTB, n = 15, 20%). Table 3 presents the tumor, treatment, and psychological characteristics for patient groups with cognitive impairment and/or cognitive concerns. Supplementary Figure 1 shows the time between diagnosis of NSCLC and study visit, disease status, and the presence of cognitive impairment or cognitive concerns for each patient.

Cognitive impairment and cognitive concerns were not directly correlated (Pearson $r = -.11$; $P = .93$), though both types of cognitive problems were present in a subset of patients (n = 10, 13%). The severity of cognitive impairment and cognitive concerns was also unrelated in patients with ($r = .02$; $P = .99$) and without brain metastases ($r = .02$; $P = .92$).

Psychological Variables

Neurobehavioral dysfunction was present in 24 patients (31%; Table 3). At least moderate depression was reported by 18 patients (23%), and 25 (33%) had demoralization (loss of meaning and purpose in life) scores above the cutoff. The median reported level of illness intrusiveness (illness-induced lifestyle disruption) was 37 (interquartile range [IQR] = 27; range: 13-71), which is similar to previously reported levels of illness intrusiveness in a lung cancer cohort[41] (n = 99; mean = 36.8; SD = 18.5). Median reported level of self-esteem was 21 (IQR = 8, range: 6-30), and this is comparable to reported self-esteem in a cohort of US adults[46] (n = 503; mean = 22.6; SD = 5.8).

Factors Associated With the Presence of Cognitive Impairment

A history of cranial irradiation was associated with the presence of cognitive impairment (odds ratio [OR] = 2.89, 95% CI 1.04-8.02, $P = .04$; Table 4). Because none of the other variables (sex, years of education, smoking history, time since mNSCLC diagnosis, presence of a targetable mutation, disease progression, or brain metastases, receiving systemic treatment, cognitive concerns, neurobehavioral concerns depression, demoralization, illness intrusiveness, self-esteem, and physical symptoms) were individually related to the presence of cognitive impairment, no multivariate analysis was performed.

Factors Associated With the Presence of Cognitive Concerns

Factors individually associated with the presence of clinically significant cognitive concerns were neurobehavioral concerns, depression, demoralization, illness intrusiveness, self-esteem, and physical symptoms (Table 5). In the multivariate model, greater illness intrusiveness (OR = 1.04, 95% CI, 1.00-1.08, $P = .03$) and lower self-esteem (OR = 0.86, 95% CI, 0.74-0.98, $P = .03$) remained significantly associated with the presence of cognitive concerns. The model, including illness intrusiveness and self-esteem,

Table 3. Patient, Treatment, and Psychological Outcomes Grouped by the Presence of Cognitive Problems

Variables	Total (N = 77)	Cognitive Impairment (n = 21)	Cognitive Concerns (n = 10)	Both Cognitive Impairment and Cognitive Concerns (n = 10)	No Cognitive Problems (n = 36)
Brain metastases	41 (53%)	12 (57%)	4 (40%)	7 (70%)	18 (50%)
Received cranial irradiation	23 (30%)	9 (43%)	3 (30%)	4 (40%)	7 (19%)
Active systemic treatment	60 (78%)	15 (71%)	8 (80%)	9 (90%)	28 (78%)
Neurobehavioral concerns (FrSBe *T*-score > 65)	24 (31%)	5 (24%)	7 (70%)	5 (50%)	7 (19%)
Depression (PHQ-9 > 10)	18 (23%)	6 (29%)	3 (30%)	5 (50%)	4 (11%)
Demoralization (DS > 30)	25 (32%)	6 (29%)	6 (60%)	6 (60%)	7 (19%)
Illness intrusiveness (median (range))	37 (13-71)	34 (13-67)	55 (23-68)	52 (32-67)	30 (18-71)
Self-esteem (median (range))	21 (6-30)	24 (14-30)	19 (17-27)	19 (6-22)	25 (9-30)

Abbreviations: DS, Demoralization Scale; FrSBe, Frontal Systems Behavior Scale; PHQ-9, Patient Health Questionnaire.
When a patient skipped an item but completed at least half of the questionnaire items, scores were prorated (ie, the sum of the individual item scores was multiplied by the total number of scale items and subsequently divided by the number of items answered by the patient).[42]

Table 4. Univariate Binary Logistic Regression Evaluating Factors Associated With the Presence of Cognitive Impairment

	Univariate		
Variables	Odds Ratio	95% CI	*P*-value
Sex (M vs F)	0.58	0.23-1.46	.25
Years of education	0.93	0.80-1.09	.39
Smoking (no vs yes)	1.49	0.54-4.12	.45
Time since metastatic NSCLC diagnosis (<10 vs ≥10 months)	1.32	0.53-3.33	.55
Targetable mutation (no vs yes)	0.53	0.17-1.68	.28
Disease progression (no vs yes)	0.67	0.25-180	.43
Brain metastases (no vs yes)	1.81	0.71-4.59	.21
Cranial irradiation (no vs yes)	**2.89**	**1.04-8.02**	**.04**
Active systemic therapy (no vs yes)	0.98	0.32-2.93	.97
Cognitive concerns (FACT-Cog PCI)	0.98	0.95-1.02	.31
Neurobehavioral concerns (FrSBe)	1.01	0.97-1.04	.68
Depression (PHQ-9)	1.03	0.95-1.14	.42
Demoralization (DS)[a]	1.00	1.00-1.01	.13
Illness intrusiveness (IIRS)	1.01	0.99-1.04	.35
Self-esteem (RSE)	0.94	0.86-1.03	.19
Physical symptoms (MSAS)	0.99	0.95-1.04	.72

Significance level of the bold variables is $P < .05$.
Abbreviations: COG-comp, cognitive composite; DS, Demoralization Scale; FACT-Cog PCI, Functional Assessment of Cancer Therapy-Cognitive Function Perceived Cognitive Impairment; FrSBe, Frontal Systems Behavior Scale; IIRS, Illness Intrusiveness Rating Scale; MSAS, Memorial Symptom Assessment Scale; NSCLC, non-small cell lung cancer; PHQ-9, Patient Health Questionnaire; RSE, Rosenberg Self-Esteem Scale.
The analyses were performed in 77 patients, in total 11 separate questionnaire scores (FACT-COG PCI = 1, FrSBe = 1, PHQ-9 = 1, DS = 3, IIRS = 2, RSE = 1, and MSAS = 2) and 1 COG-comp were missing.
[a]The Box-Tidwell procedure demonstrated the lack of a linear relationship between demoralization and its logit. When including a 2-power term of demoralization, a linear relationship between squared-demoralization and its logit was observed.

was statistically significant ($X^2(2) = 17.5$; $P < .001$) and correctly classified 73% of the cases.

Discussion

In this cross-sectional study of cognitive problems in patients with mNSCLC, cognitive impairment and cognitive concerns were common in those with and without brain metastases. Cognitive impairment and cognitive concerns were not necessarily linked in these individuals. Those who had received cranial irradiation for their brain metastases were most at risk for cognitive impairment, whereas cognitive concerns tended to be associated with greater illness intrusiveness and lower self-esteem. These findings direct attention to the impact of radiation on cognition, an important determinant of quality of life, and the psychological consequences of mNSCLC, which might be amenable to intervention.

Approximately half of the patients in our study met ICCTF criteria[35] for cognitive impairment. Previous studies found cognitive impairment rates of 30% to 71% in non-metastatic NSCLC[11–15] and rates of 50% to 75% in unselected cancer patients with newly diagnosed brain metastases.[19–21] The wide range in prevalence of cognitive impairment reported in these studies might be due to differences in neuropsychological tests used, definitions of cognitive impairment, and different time points in the disease trajectory at which cognitive problems were assessed. The novelty of the current study lies in the inclusion of patients with mNSCLC with and without brain metastases, and demonstration of the frequency of both cognitive concerns and cognitive impairment in this vulnerable patient population.

Patients with a history of cranial irradiation were most at risk for cognitive impairment in the present study. Large randomized trials have shown that the prevalence and rate of cognitive decline are higher in those treated with WBRT compared with those who receive SRT alone.[23,24,26] Although patients treated with SRT have shown only mild to no decline in neurocognitive functioning after SRT in some studies,[25,47] there is also evidence of cognitive decline after SRT,[23,26] and a proportion of those treated with SRT already show cognitive impairment even before treatment.[21] The reported differences between WBRT and SRT in the frequency of cognitive impairment might not only be due to less toxicity associated with SRT but could also be due to differences in the volume or number of brain metastases of the patients.

The presence of brain metastases was not directly related to the presence of cognitive impairment in our study, and patients with and without brain metastases had cognitive impairment. In other studies, brain metastasis volume was more predictive of cognitive impairment than the

Table 5. Univariate and Multivariate Binary Logistic Regression Evaluating Factors Associated With the Presence of Cognitive Concerns Impairment

	Univariate			Multivariate		
Variables	Odds Ratio	95% CI	*P*-value	Odds Ratio	95% CI	*P*-value
Sex (M vs F)	1.31	0.47-3.66	.61			
Years of education	0.91	0.76-1.09	.33			
Smoking (no vs yes)	1.42	0.45-4.52	.55			
Time since metastatic NSCLC diagnosis (<10 vs ≥10 months)	1.40	0.50-3.94	.53			
Targetable mutation (no vs yes)	1.26	0.33-4.85	.74			
Disease progression (no vs yes)	1.14	0.39-3.34	.82			
Brain metastases (no vs yes)	1.14	0.41-3.17	.81			
Cranial irradiation (no vs yes)	1.35	0.45-3.99	.59			
Active systemic therapy (no vs yes)	1.89	0.48-7.42	.36			
Cognitive impairment (COG-comp)	1.00	0.95-1.07	.89			
Neurobehavioral concerns (FrSBe)	1.07	1.02-1.12	.003	1.02	0.97-1.08	.42
Depression (PHQ-9)	1.19	1.05-1.34	.005	1.06	0.88-1.26	.56
Demoralization (DS)	1.05	1.00-1.08	.01	0.97	0.92-1.03	.33
Illness intrusiveness (IIRS)	**1.06**	**1.02-1.10**	**.001**	**1.04**	**1.00-1.08**	**.03**
Self-esteem (RSE)	**0.81**	**0.71-0.93**	**.002**	**0.86**	**0.74-0.98**	**.03**
Physical symptoms (MSAS)	1.07	1.02-1.13	.01	1.01	0.94-1.08	.88

Significance level of the bold variables is $P < .05$.
Abbreviations: COG-comp, cognitive composite; DS, Demoralization Scale; FACT-Cog PCI, Functional Assessment of Cancer Therapy-Cognitive Function Perceived Cognitive Impairment; FrSBe, Frontal Systems Behavior Scale; IIRS, Illness Intrusiveness Rating Scale; MSAS, Memorial Symptom Assessment Scale; NSCLC, non-small cell lung cancer; PHQ-9, Patient Health Questionnaire; RSE, Rosenberg Self-Esteem Scale.
The analyses were performed in 77 patients; in total, 11 separate questionnaire scores (FACT-COG PCI = 1, FrSBe = 1, PHQ-9 = 1, DS = 3, IIRS = 2, RSE = 1, and MSAS = 2) and 1 COG-comp were missing.

presence or number of brain metastases[22,25]; this was not assessed in the current study. Furthermore, our cohort had a higher percentage of patients with an *EGFR* or *ALK* mutation, likely due to the higher percentage of nonsmokers,[48] Asian patients,[49] and patients with brain metastases[50] in the study sample. The intracranial efficacy of newer targeted agents in NSCLC patients with targetable mutations may also influence the relationship between brain metastases and cognitive problems and merits further investigation.

Cognitive concerns were common in our study population and were associated with greater illness intrusiveness and decreased self-esteem. Illness intrusiveness is defined as the disease-related disruption in daily living, valued activities, and interests, and has been associated with poorer quality of life in patients with cancer.[41,51] Cognitive concerns may increase illness intrusiveness, as it can prevent patients from working or limit social and familial relationships. Those activities have also been found to be essential to sustain personal and social identity and self-esteem during and after the cancer experience.[52,53] Therefore, individuals who experience cognitive concerns may also lose self-esteem due to disruptions in their work, social, and family roles. Conversely, lower self-esteem may adversely affect an individual's experienced cognitive concerns. Ultimately, understanding the relationships between cognitive concerns and illness intrusiveness and self-esteem may lay the groundwork for novel cognitive rehabilitation strategies focusing on retaining engagement in valued activities and bolstering self-esteem.

The lack of association between cognitive impairment and cognitive concerns previously observed in other tumor types was also observed in our mNSCLC cohort.[27–29] The lack of concordance between cognitive impairment on neuropsychological tests and reported cognitive concerns may be due to the lack of insight of patients regarding cognitive impairment or to differences in the constructs captured by neuropsychological tests and by self-reported questionnaires.[27] Self-report questionnaires assessing cognitive problems may reflect the perceived impact of cognitive impairment on daily functioning and changes in functioning, which are not necessarily captured by neuropsychological tests. This underscores the importance of collecting both types of measures in future research. Moreover, the lack of relation between cognitive impairment and cognitive concerns is clinically relevant for physicians treating patients with mNSCLC. Those patients may report concerns about cognitive decline without showing signs of decline on standardized neuropsychological tests and may benefit from attention to illness intrusiveness and self-esteem, in addition to cognitive rehabilitation strategies.

Limitations of our study include the small sample size and cross-sectional design, which prevented us from exploring the effects of WBRT, SRT, and different

systemic treatments (targeted agents, immunotherapy, and chemotherapy) on changes in cognitive problems over time. Secondly, we lacked information regarding brain metastases volume, which may influence cognitive impairment. Cognitive problems are multifactorial in origin, and many factors could contribute to cognitive problems. Some of these factors were not included in the current study, such as medication usage and the presence of seizures, and warrant further investigation. Sampling bias may also have affected our findings; patients with relatively good performance status may have been overrepresented in the current study since patients had to attend the study visit in person to complete the study measures. The inclusion of patients with relatively good performance status could have led to the lower prevalence rate of cognitive impairment and cognitive concerns in our sample, as patients with more advanced disease or functional difficulties may suffer from greater cognitive problems. Longitudinal studies in larger samples of patients with mNSCLC with and without brain metastases are needed to further examine cognitive problems and the impact of patient, tumor factors, and (systemic and localized) antitumor treatment on cognitive problems.

In conclusion, in patients with mNSCLC with and without brain metastases, cognitive impairment and cognitive concerns were common, but the former may be more directly related to cranial irradiation and the latter to illness intrusiveness and self-esteem. These findings suggest that cognitive rehabilitation interventions in this population should focus not only on cognitive skills and strategy training but also on reducing illness intrusiveness and the preservation of self-esteem.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Practice*.

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