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LETTER TO THE EDITOR

Association between anxiety and depression symptoms and completion of first-line treatment in newly diagnosed lung cancer patients

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Background

Poor adherence to cancer treatment is commonly seen [1–3] with consequences including worse overall survival and quality of life [2]. In line with this, almost half (46%) of lung cancer patients did not receive optimal first-line treatment in a Danish nationwide cohort study [4], which was associated with comorbidity, and socioeconomic resources amongst others. Depression has been identified as a risk factor for non-compliance to non-cancer medical treatment in a meta-analysis [5]. Psychological symptoms like depression and anxiety are prevalent among cancer patients [6] and studies show that this is especially so for lung cancer patients [7–9]

However, research on the link between anxiety and depression on treatment adherence among lung cancer patients is scarce. Two small prospective studies of non-small cell lung cancer patients (NSCLC) ($n = 50$–82) reported, that depression was associated with reduced treatment adherence [2] and that anxiety symptoms were associated with reduced adherence to chemotherapy defined as a dose delay or reduction [3]. Greer et al. [3] concluded, that further research is needed to clarify the underlying mechanisms of the association between psychological factors and chemotherapy adherence.

The aim of this prospective cohort study was to investigate the associations of anxiety and depression symptoms, measured by The Hospital Anxiety and Depression Scale (HADS) [10], with the completion of first-line treatment in newly diagnosed lung cancer patients in Denmark.

Material and methods

This study is part of the PACO2 study investigating the prevalence, determinants and disparities in receipt of first-line treatment in lung cancer patients. Newly diagnosed non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) patients referred for first-line treatment at the Oncology Department at Herlev University Hospital from September 2016 to September 2017 were invited to participate in the study. To be included, patients had to be literate in Danish and to have an Eastern Cooperative Oncology Group (ECOG) performance status [11] of ≤ 2. All disease stages were eligible. The questionnaire consisted of validated scales measuring physical and psychological health, self-efficacy, supportive care needs and study-specific questions on sociodemography and lifestyle. Only results on anxiety and depression are reported here. Results on Health-Related Quality of Life [12] and self-efficacy [13] have been published [12,13]. The study was approved by the Danish Data Protection Agency (2015–41–4236) and registered in the Danish Cancer Society Research Database (2019–DCRC–0062). The PACO2 study protocol was however not publicly registered. Informed consent was obtained from all participants. No biological material was included in the project and the study did not require approval from the Committee on Health Research Ethics.

Measures

Symptoms of anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS) [10], a clinical screening tool designed as a brief self-assessment scale used to detect symptoms of anxiety and depression in somatically ill patients [14,15]. It is recommended that clinicians proceed with clinical assessment in order to offer appropriate treatment or referral if anxiety and/or depression is identified by use of the scale [16].

HADS consists of two subscales assessing anxiety and depression symptoms within the past week and consists of 14 items with 7 items for each subscale [14]. Score ranges are used to identify severity in each subscale (0–7 points = normal, 8–10 points = mild, 11–14= moderate, 15–21 = severe) [14]. The reliability of the HADS applied on cancer patients has shown adequate internal consistency with a Crohbach's alpha value of 0.87 for the total of the 14 items of the scale, a value of 0.76 for the anxiety subscale and 0.84

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for the depression subscale [17]. We dichotomised the scores (anxiety or depression symptoms yes/no) by the cut-off score of $\geq$8 on each subscale to identify patients with potential anxiety or depression [18]. Self-reported education was dichotomised into short or medium (mandatory school, secondary high school and vocational education; $\leq$12 years of education) and long (higher education; >12 years of education). Cohabitation status was categorised as living with a partner (cohabiting or married) or living alone. Lifestyle factors including smoking (current or former/never smoker) and alcohol consumption as none (0 units per week), 1–7/14 units per week or 8/15+ units per week (exceeds recommendations) for women/men in accordance with national recommendations [19]. BMI was calculated by height and weight and grouped into underweight (<18.5 kg/m^2), normal weight (18.5−24.9 kg/m^2), overweight (25–29.9 kg/m^2) or obese ($\geq$30 kg/m^2)[20].

Information on clinical factors such as disease stage based on the TNM classification system, ECOG Performance status [11], comorbidity (counted as a number of chronic conditions categorised as 0, 1 or $\geq$2), and type of lung cancer (NSCLC or SCLC).

Completion of first-line lung cancer treatment

Data on patients' first-line treatment plans (both curative and palliative intent), complications during treatments, dose reductions and dose delays were obtained from the patient's medical records. First-line treatment consisted of chemotherapy alone or combined with radiotherapy, immunotherapy or different combinations hereof. Deviations from the planned first-line treatment were defined as either omission or $\geq$20% reduction in one or more chemotherapy doses, omission of one or more radiotherapy sessions or omission of planned lobectomy (only curative intent). All deviations were recorded and each counted equally. Completion of first-line treatment was categorised as a binary variable (yes, no). Reasons for non-completion of treatment were registered (toxicity, lack of attendance, progression of disease or death).

Statistical methods

Analyses were performed separately for patients with anxiety and depression symptoms. We used logistic regression models to measure the influence of anxiety and depression symptoms on the likelihood of non-completion of first-line treatment, measured as odds ratio (ORs) with 95% confidence intervals (CIs). Multivariate logistic regression models were performed adjusting for confounders in three steps: firstly, adjusting for age and gender, secondly, further for stage, performance status and comorbidity, and thirdly additionally for education, cohabitation status, smoking, alcohol consumption and BMI. No formal power calculation was conducted for these analyses. Analyses were conducted with SAS (version 9.4).

Results

Patient characteristics

A total of 137 lung cancer patients participated in the study of which 135 patients completed the HADS. The age ranged from 50-91 years with a mean age of 68.9 years (SD 7.37) and with an equal sex distribution. Overall, 72 (53%) patients completed their first-line treatment as planned. Among patients who completed their first-line treatment, 44 (61%) had performance status 0 and 26 (36%) had more than two chronic conditions compared to 27 (44%) and 31 (49%), respectively, among patients that did not complete the treatment (Table 1).

Anxiety symptoms

Forty-seven (35%) of the patients had HADS scores 8–14 (mild to moderate anxiety symptoms) while no patients scored 15 or above (severe anxiety symptoms) pre-treatment. Among patients that completed first-line treatment, 13 (18%) had HADS scores 8–10 (mild anxiety symptoms) compared to 22 (35%) in patients that did not complete treatment (Table 1). Patients with anxiety symptoms were more likely to not complete their first-line treatment than patients with no anxiety, with an OR of 2.24 (95% CI 1.08–4.71) adjusted for age and gender. However, failing to obtain statistical significance when fully adjusted, (OR, 1.97; 95% CI 0.79–5.02) (Table 2).

Depression symptoms

Twenty-two (16%) patients had HADS scores 8–14 (mild to moderate depression symptoms) while no patients scored 15 or above (severe depression symptoms) at baseline. Among patients that completed first-line treatment, four (6%) had HADS scores 8–10 (mild depression symptoms) and none scored 11–14 (moderate depression symptoms), while corresponding numbers were 19% and 10% among patients that did not complete their treatment (Table 1). Patients with depression symptoms were almost 7-fold more likely to not complete their first-line treatment than patients with no depression (OR, 7.0; 95% CI 2.39–25.84) and in the fully adjusted model this association was even stronger (OR, 12.36; 95% CI 3.23–60.79) although the CIs were wide (Table 2).

Discussion

In this prospective cohort study of 135 newly diagnosed lung cancer patients referred for oncological treatment, almost half (47%) of the patients did not complete the planned first-line treatment. Having mild to moderate depression symptoms was strongly associated with not completing first-line treatment compared to patients with no depression symptoms after adjustment for stage, health status, socio-economic and lifestyle factors. Anxiety symptoms were also associated with not completing first-line treatment, although failing to reach statistical significance after adjustments.

Table 1. Descriptive characteristics of 135 newly diagnosed lung cancer patients referred for oncological treatment at University Hospital Herlev, Denmark, 2016–2017.

Patient characteristics	Total *Number (%)*	Completion of first-line treatment *Number (%)*	Non-completion of first-line treatment *Number (%)*	*p*-value
Total	135 (100)	72 (53)	63 (47)	
Age at diagnosis (years)				0.78
Mean age	68.9 (SD: 7.37)			
Gender				0.68
Male	69 (51)	38 (53)	31 (49)	
Female	66 (49)	34 (47)	32 (51)	
ECOG performance status				0.03
0	71 (53)	44 (61)	27 (44)	
1	52 (39)	26 (36)	26 (43)	
2	10 (8)	2 (3)	8 (13)	
Missing	*2*		2	
Disease stage[a]				0.60
Early/Medium	74 (55)	41 (57)	33 (52)	
Advanced	61 (45)	31 (43)	30 (48)	
Comorbidity (no. of chronic conditions)				0.11
0	32 (24)	22 (31)	10 (16)	
1	46 (34)	24 (33)	22 (35)	
$\geq$2	57 (42)	26 (36)	31 (49)	
Type of lung cancer				0.30
Small cell lung cancer	21 (16)	9 (13)	12 (19)	
Non-small cell lung cancer	114 (84)	63 (87)	51 (81)	
Type of treatment				0.22
Curative	60 (47)	36 (51)	24 (41)	
Palliative	69 (53)	34 (49)	35 (59)	
Missing	6	2	4	
Smoking				0.10
Never or former smokers	105 (79)	53 (74)	52 (85)	
Current smokers	28 (21)	19 (26)	9 (15)	
Missing	2		2	
Alcohol consumption per week (women/men)				0.15
None	47 (36)	26 (37)	21 (35)	
>1 and $\leq$7/14	58 (44)	27 (38)	31 (52)	
$\geq$8/15	26 (20)	18 (25)	8 (13)	
Missing	4	1	3	
BMI				<0.05
Underweight (<18.5 kg/m^2)	11 (8)	7 (10)	4 (7)	
Normal weight (18.5−24.9 kg/m^2)	58 (44)	39 (54)	19 (31)	
Overweight (25–29.9 kg/m^2)	45 (34)	15 (21)	30 (49)	
Obese ($\geq$30 kg/m^2)	19 (14)	11 (15)	8 (13)	
Missing	2		2	
Level of education				0.64
Short, medium or other (< =13 years)	56 (42)	31 (44)	25 (40)	
Long (>13 years)	78 (58)	40 (56)	38 (60)	
Missing	1	1		
Cohabitation status				0.96
Living with a partner	94 (70)	50 (69)	44 (70)	
Living alone	41 (30)	22 (31)	19 (30)	
HADS score, Anxiety				0.07
Normal (0–7 points)	88 (65)	53 (74)	35 (56)	
Mild (8–10 points)	35 (26)	13 (18)	22 (35)	
Moderate (11–14 points)	12 (9)	6 (8)	6 (9)	
Severe (15–21 points)	–	–	–	
HADS score, Depression				<0.001
Normal (0–7 points)	113 (84)	68 (94)	45 (71)	
Mild (8–10 points)	16 (12)	4 (6)	12 (19)	
Moderate (11–14 points)	6 (4)	–	6 (10)	
Severe (15–21 points)	–	–	–	

[a]NSCLC: Early stage: T1-3, N0, M0. Medium stage: T1-4, N0-3, M0. Advanced stage: Any T, any N, M1.
SCLC: Early stage: limited disease (M0). Advanced stage: Extended disease (M1).

Depression is associated with poor medical treatment adherence in patients in general [5]. In a study [2] of 82 NSCLC patients, it was found that depression was significantly associated with reduced treatment adherence. A total of 58% of the depressed patients stopped attending appointments versus 42% of the patients without depression [2].

Adjusting for disease- and health-specific factors seemed to lower slightly the risk estimate for both anxiety and depression symptoms in our study indicating that poor and potentially declining health status is associated with psychological symptoms like depression and anxiety. This may reflect both psychological reactions to serious disease and to declining functioning [2,21] but also potentially reflect progression in the lung cancer disease biologically leading to affective symptoms such as anxiety and depression [22,23].

Table 2. Odds ratios for non-completion of first-line treatment in 135 newly diagnosed lung cancer patients with mild/moderate anxiety and/or depression symptoms.

HADS	*n*	Unadjusted OR (95% CI)	*n*	Model 1a OR (95% CI)	*n*	Model 2b OR (95% CI)	*n*	Model 3c OR (95% CI)
No anxiety	88	1.0 (ref.)	88	1.0 (ref.)	88	1.0 (ref.)	81	1.0 (ref.)
Anxiety symptoms	47	2.32 (1.09 −4.65)	47	2.24 (1.08–4.71)	45	1.97 (0.90–4.36)	45	1.97 (0.79–5.02)
No depression	113	1.0 (ref.)	113	1.0 (ref.)	112	1.0 (ref.)	105	1.0 (ref.)
Depression symptoms	22	6.80 (2.36–24.72)	22	7.0 (2.39–25.84)	21	5.76 (1.85– 22.11)	21	12.36 (3.23–60.79)

CI: confidence interval; OR: odds ratio; n: number; anxiety symptoms, mild or moderate; no anxiety, normal; depression symptoms, mild or moderate; no depression, normal.
[a]Adjusted for age and gender, $n = 135$.
[b]Adjusted for age, gender, stage, performance status and comorbidity, $n = 133$.
[c]Adjusted for age, gender, stage, performance status, comorbidity, level of education, cohabitation status, smoking, alcohol consumption and BMI, $n = 126$.

Our results on the association between anxiety symptoms and non-completion of first-line treatment did not reach statistical significance in fully adjusted analysis possibly due to low statistical power and thus, results should be interpreted cautiously. Still, our results support findings from a US study [3] where anxiety symptoms measured by a HADS score of $\geq$8 was a predictor of poor chemotherapy adherence among 15 (31%) NSCLC patients [3].

A review reported, that on average, one in four lung cancer patients had experienced periods of depression or other psychological disorders while diagnosed with lung cancer [24], and suggested that screening and treatment of depression patients should be offered to improve the quality of care [24]. Based on our findings, we suggest that future research should investigate interventions screening newly referred lung cancer patients for depression and anxiety, and initiate diagnostic evaluation and relevant psychological and/or pharmacological treatment if necessary in order to improve psychological well-being among patients. Such a systematic approach could potentially contribute to more lung cancer patients completing first-line cancer treatment. This would be in line with other studies, arguing for the importance of assessing symptoms of depression and anxiety in the initial evaluation of lung cancer patients, in order to implement strategies to control these symptoms, which may improve adherence to treatment and contribute to improved overall survival and quality of life [23,25].

The strengths of our study include the prospective study design, inclusion of newly diagnosed lung cancer patients, detailed information obtained on the patient's disease, treatment, general health and comorbidity from medical records, as well as the patient-reported information obtained from study-specific questionnaires and validated scales as the HADS. We included both SCLC and NSCLC patients thereby representing the clinical reality.

Limitations of our study include the limited statistical power due to few cases with mild to moderate anxiety or depression symptoms. One might have explored if treatment intent was modifying the association between depression or anxiety and completion of treatment, however, we did not have sufficient power for separate analyses. Another potential limitation is that we only analyse depression and anxiety. Although adjusting for proxies for physical health by including confounder adjustment for performance status and comorbidity, other psychological factors and their interactions on the adherence to first-line treatment would have been relevant to explore but was not possible due to the small sample size and low statistical power. The single-site study may affect generalisability of the results to the source population. Future studies should include more patients leading to better statistical power to verify and expand the results of our study.

Conclusion

In this prospective cohort study among newly referred lung cancer patients, patients with mild to moderate depression symptoms were less likely to complete first-line treatment. Health care professionals treating lung cancer patients should be aware of the impact of depression symptoms on the completion of first-line treatment and future research should investigate if tailored strategies assessing and treating if necessary, depression symptoms among newly referred lung cancer patients may reduce non-adherence to first-line lung cancer treatment.

Author contributions

SOD conceived the study and was the grant holder. TKK and SOD conceptualised and designed the study. TKK conducted the research. JMH wrote this manuscript. JMH, TKK, SOD, AM, MCO, IA participated in data analysis, interpretation and description of the results. All authors contributed to manuscript preparation and approved the final manuscript.

Ethics declarations & trial registry information

The study was approved by the Danish Data Protection Agency (2015 − 41 − 4236) and registered in the Danish Cancer Society Research Database (2019 – DCRC − 0062). Informed consent was obtained from all participants in the study. As no human biological material was included in the project, the study did not require approval from the Committees on Health Research Ethics for the Capital Region of Denmark.

Patient consent

Informed consent was obtained from all participants in the study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The authors agree to share anonymized data upon reasonable request by researchers.

References

[1] Hansen LA. Best practices in maximizing adherence to cancer therapy The Oncology Pharmacist. Forthcoming [02.10.2022]. available at [https://www.theoncologypharmacist.com/ton-online-first/3695-ton-3695]
[2] Arrieta Ó, Angulo LP, Núñez-Valencia C, et al. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. Ann Surg Oncol. 2013;20(6):1941–1948.
[3] Greer JA, Pirl WF, Park ER, et al. Behavioral and psychological predictors of chemotherapy adherence in patients with advanced non-small cell lung cancer. J Psychosom Res. 2008;65(6):549–552.
[4] Dalton SO, Steding-Jessen M, Jakobsen E, et al. Socioeconomic position and survival after lung cancer: influence of stage, treatment and comorbidity among Danish patients with lung cancer diagnosed in 2004–2010. Acta Oncol. 2015;54(5):797–804.
[5] DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000;160(14):2101–2107.
[6] Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol. 2011;12(2):160–174.
[7] Lee Y, Lin P-Y, Lin M-C, et al. Morbidity and associated factors of depressive disorder in patients with lung cancer. Cancer Manag. 2019;11:7587.
[8] Brintzenhofe-Szoc KM, Levin TT, Li Y, et al. Mixed anxiety/depression symptoms in a large cancer cohort: prevalence by cancer type. Psychosomatics. 2009;50(4):383–391.
[9] Walker J, Hansen CH, Martin P, et al. Prevalence, associations, and adequacy of treatment of major depression in patients with cancer: a cross-sectional analysis of routinely collected clinical data. Lancet Psychiatry. 2014;1(5):343–350.
[10] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361–370.
[11] Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern cooperative oncology group. Am J Clin Oncol. 1982;5(6):649–656.
[12] Levinsen AKG, Dalton SO, Andersen I, et al. Association between health-related quality of life and completion of first-line treatment among lung cancer patients. Cancers. 2022;14(14):3343.
[13] Kjaer TK, Hansen NHG, Levinsen AKG, et al. The association between self-efficacy and completion of first-line treatment among newly referred patients with lung cancer. J of Psychosocial Oncology Research and Practice. 2022;4(3). doi:10.1097/OR9.0000000000000079
[14] Zigmond AS, Snaith RP. The HADS: hospital anxiety and depression scale. Windsor: NFER Nelson: 1994.
[15] Fayers PM, Machin D. Quality of life: the assessment, analysis and reporting of patient-reported outcomes. John Wiley & Sons; 2015.
[16] Mitchell AJ, Meader N, Symonds P. Diagnostic validity of the hospital anxiety and depression scale (HADS) in cancer and palliative settings: a meta-analysis. J Affect Disord. 2010;126(3):335–348.
[17] Villoria E, Lara L. Assessment of a hospital anxiety and depression scale for cancer patients. Rev Med Chil. 2018;146(3):300–307.
[18] Bjelland I, Dahl AA, Haug TT, et al. The validity of the hospital anxiety and depression scale: an updated literature review. J Psychosom Res. 2002;52(2):69–77. .
[19] Sundhedsstyrelsen [Danish Health Authority]. Forebyggelsespakke alkohol [prevention. Alcohol]. The Danish Health Authority: Denmark; 2018. Danish.
[20] World Health O. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. Geneva: 2000. (WHO Technical Report Series; 894).
[21] Savitz DA, Wellenius GA. Interpreting epidemiologic evidence: connecting research to applications. New York (NY): Oxford University Press; 2016.
[22] Marschner N, Zacharias S, Lordick F, et al. Association of disease progression with health-related quality of life among adults with breast, lung, pancreatic, and colorectal cancer. JAMA Netw Open. 2020;3(3):e200643.
[23] Reis JC, Antoni MH, Travado L. Emotional distress, brain functioning, and biobehavioral processes in cancer patients: a neuroimaging review and future directions. CNS Spectr. 2020;25(1):79–100.
[24] Carlsen K, Jensen AB, Jacobsen E, et al. Psychosocial aspects of lung cancer. Lung Cancer. 2005;47(3):293–300.
[25] Andersen BL, Valentine TR, Lo SB, et al. Newly diagnosed patients with advanced non-small cell lung cancer: a clinical description of those with moderate to severe depressive symptoms. Lung Cancer. 2020;145:195–204.