

[ORIGINAL ARTICLE]

Performance Status Is a Risk Factor for Depression before the Diagnosis of Lung Cancer Patients

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Abstract:

Objective Previous studies have shown that lung cancer patients experience depression before their diagnosis. However, the patient characteristics that are risk factors for depression before the diagnosis of lung cancer are unclear. We therefore performed this study to identify the characteristics that are risk factors for depression in lung cancer patients.

Methods We performed a prospective observational study that included 183 patients who visited our department for suspected lung cancer between August 2014 and March 2017. These patients completed a Quick Inventory of Depressive Symptomatology-Self Report questionnaire. Ten patients with a history of depression were excluded.

Results Among the remaining 173 patients, 110 were diagnosed with lung cancer. Among these 110 patients, 57 had depression. A poor performance status (PS) was significantly more prevalent in patients with depression than in those without. Furthermore, a multivariate analysis revealed that a poor PS was the only independent risk factor for depression before the diagnosis of lung cancer.

Conclusion Physicians can use this information to evaluate whether patients have depression before the diagnosis of lung cancer.

Key words: depression, lung cancer, performance status, before diagnosis, self-report questionnaire

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Introduction

Approximately 40% of all cancer patients are reported to be complicated with depression (1). Several studies have also shown that 12-46% of patients with lung cancer, which is the most common cause of cancer-related death worldwide, experienced depression (2-7). Moreover, 16-63% of patients were already complicated with depression before the diagnosis of lung cancer (8-10). Previous studies found that the adherence to treatment (11), quality of life (12), and prognosis were poorer (3, 7, 13, 14) in cancer patients with depression than in those without. These observations imply the need to identify predictors of depression before the diagnosis of lung cancer in lung cancer patients. To date, the re-

ported risk factors for depression after the diagnosis of lung cancer include a poor performance status (PS), cancer-related pain, and advanced stage (4, 5, 15). On the other hand, there has only been one study of depression before the diagnosis of lung cancer; this showed that a poor PS, advanced stage, and a history of mental disorder are risk factors for depression (8). However, no study identified which of these were independent risk factors using a multivariate analysis, or whether patient characteristics such as sex, age, and social factors were risk factors.

Depression before the diagnosis of breast cancer is reported to be associated with a decreased standard treatment induction rate in breast cancer patients (16, 17); however, there have been no similar investigations among lung cancer patients.

Table 1. Patient Characteristics.

Characteristic	Lung cancer n=110
Sex	
Female/male	33/77
Age (years)	
Median (range)	70 (27-88)
Histology	
Ad/Sq/Sm/LCNEC/Pleo/NSCLC	74/19/14/1/1/1
Clinical stage	
Inoperable IIIA-IV/I-operable IIIA	52/58
ECOG PS	
0/1/2/3/4	82/18/10/0/0
Smoking history	
Positive/negative/unknown	79/30/1
Symptoms	
Positive/negative	47/63
Marital status	
Married/single/divorced or separated/unknown	85/6/16/3
Occupation	
Retired/unemployed/employed/unknown	48/6/40/16
QIDS-SR score	
Mean±SD	6.2±4.5
Depression	
Positive/negative	57/53

Ad: Adenocarcinoma, Sq: Squamous cell carcinoma, Sm: Small cell carcinoma, LCNEC: Large cell neuroendocrine carcinoma, Pleo: Pleomorphic carcinoma, NSCLC: non-small cell lung cancer, ECOG PS: Eastern Cooperative Oncology Group performance status

We therefore performed this prospective study to identify the characteristics of lung cancer patients that are risk factors for depression using multiple logistic regression models, and to determine whether depression is associated with the initial treatment induction rate of lung cancer patients.

Materials and Methods

Participants and study design

We enrolled consecutive patients who visited our department at Hiroshima University Hospital between August 2014 and March 2017 for suspected lung cancer following radiological examinations at other hospitals. Those enrolled agreed to complete the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) questionnaire. Patients with a history of mental disorder were excluded from the study. The enrolled patients were screened for depression using the QIDS-SR, and their clinical characteristics (sex, age, PS, smoking history, status of lung cancer, symptom, marital status and occupation) were noted at their initial visit to our department. The clinical data were evaluated by attending physicians and reviewed by investigators (K.M. and T.M.). Moreover, we determined the initial treatment induction rate in patients diagnosed with lung cancer.

This study was approved by the Hiroshima University In-

stitutional Review Board (No. E186), and was conducted in accordance with the ethical standards established by the Helsinki Declaration of 1975. Written informed consent or opt-out methods were applied in this study to obtain consent from the patients.

Questionnaires

The self-reporting QIDS-SR questionnaire includes 16 questions concerning depression and is also used during screening to determine the severity of depressive symptoms (18). This method incorporates a portion of the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) criteria, which are used to diagnose major depressive disorder worldwide (19), and has a high correlation with the Hamilton Depression Rating Scale, which is an interview-type depression symptom rating scale administered by clinicians that is commonly used to determine the level of depression (20). Previous studies have used this scale to assess depression in patients with physical symptoms, including cancer patients (21-23). The QIDS-SR score ranges from 0 to 27 points, and patients are classified as normal [0~5], mild [6~10], moderate [11~15], severe [16~20], and very severe [21~27] (18). In our study, a score of ≥ 6 points was defined as depression-positive.

Statistical analysis

Patient characteristics were compared between 2 groups using either the chi-squared test or Wilcoxon rank sum test. The results are expressed as the median (range) or mean \pm standard deviation (SD). Univariate and multivariate analyses using a logistic regression model were used to identify risk factors for depression and initial treatment adherence. For the multivariate analysis, factors were selected using a stepwise method. P values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the JMP Pro software program (version 12, SAS Institute, Cary, USA).

Results

Patient characteristics

A total of 183 patients were enrolled in the study. Ten patients who had a history of depression were excluded; hence, 173 patients were analyzed. Ultimately, 110 of these 173 patients were pathologically diagnosed with lung cancer; their clinical characteristics are shown in Table 1. Seventy percent of the 110 lung cancer patients were men. Furthermore, 52.7% had stage I to operable IIIA disease, while 47.3% had inoperable stage IIIA to IV disease. Most patients had an Eastern Cooperative Oncology Group PS score of 0 (74.5%); 16.4% had a PS score of 1 and the remainder (9.1%) had a PS score of 2. Furthermore, 72.5% of the patients were smokers, and 42.7% had chest symptoms such as coughing or shortness of breath due to lung cancer. Fifty-seven lung cancer patients (51.8%) were diagnosed with de-

Table 2. Comparison of the Characteristics of Patients with Lung Cancer with or without Depression at the Time of Their First Visit to the Hospital.

Patient characteristics	With depression n=57	Without depression n=53	p value
Sex			
Female/male	21/36	12/41	0.104
Age (years)			
Median (range)	70 (27-88)	70 (35-88)	0.912
Clinical stage			
Inoperable IIIA-IV/I-operable IIIA	33/24	19/34	0.021
ECOG PS			
≥2/0-1	9/48	1/52	0.011
Smoking amount, pack-years			
Median (range)	30 (0-159)	32.5 (0-202.5)	0.939
Symptoms			
Positive/negative	28/29	19/34	0.159
Marital status			
Married/divorced, separated, or single (n=107)	45/11	40/11	0.806
Occupation			
Retired or unemployed/employed (n=94)	25/22	29/18	0.404

CI: confidence interval, ECOG PS: Eastern Cooperative Oncology Group performance status

Table 3. Risk Factors for Depression.

	Univariate analysis			Multivariate analysis		
	Odd ratio	95% CI	p value	Odd ratio	95% CI	p value
Age (years)						
≥75/<75	1.267	0.563-2.885	0.568			
Sex						
Female/male	1.993	0.872-4.715	0.103	2.233	0.939-5.520	0.069
Clinical stage						
Inoperable IIIA-IV/I-operable IIIA	2.461	1.150-5.384	0.020	2.035	0.901-4.079	0.088
ECOG PS						
≥2/0-1	9.750	1.737-183.157	0.007	6.799	1.107-131.983	0.037
Smoking history						
Positive/negative	0.784	0.332-1.822	0.573			
Symptoms						
Positive/negative	1.728	0.808-3.750	0.159			
Marital status						
Married/divorced, separated, or single	1.125	0.437-2.901	0.806			
Occupation						
Retired or unemployed/employed	0.705	0.308-1.600	0.404			

CI: confidence interval, ECOG PS: Eastern Cooperative Oncology Group performance status

pression. Of the 63 patients diagnosed with diseases other than lung cancer, 41 had benign lung diseases, such as inflammation, 5 had lung metastasis from other cancers, and 17 patients had unconfirmed diagnoses.

Comparison of the clinical characteristics between patients with and without depression before the diagnosis of lung cancer

We compared the clinical data of patients with and without depression (Table 2). The proportion of patients with advanced inoperable lung cancer and a poor PS were significantly higher among with depression than among those

without. On the other hand, there were no significant differences between the 2 groups in other investigated characteristics. The results of logistic regression analyses of the risks of depression are shown in Table 3. The univariate analyses revealed that inoperable lung cancer and a poor PS were significant risk factors for depression. The multivariate analysis revealed that a poor PS was the only independent risk factor for depression before the diagnosis of lung cancer (Table 3).

Table 4. Comparison of Patient Characteristics with vs. without Anti-cancer Treatment.

Patient characteristics	Patients receiving anti-cancer treatment, n=104	Patients not receiving anti-cancer treatment, n=6	p value
QIDS-SR score			
Mean±SD	6.1±0.4	7.3±1.9	0.366
Age (years)			
Median (range)	70 (27-88)	75 (66-88)	0.138
Sex			
Female/male	31/73	2/4	0.855
Clinical stage			
Inoperable IIIA-IV/I-operable IIIA	47/57	5/1	0.069
ECOG PS			
≥2/0-1	9/95	1/5	0.507
Smoking history, pack-years			
Median (range)	30 (0-202.5)	69 (0-93)	0.193
Symptoms			
Positive/negative	41/63	6/0	0.004
Marital status			
Married/divorced, separated, or single (n=107)	82/21	3/1	0.823
Occupation			
Retired or unemployed/employed (n=94)	48/40	6/0	0.029

CI: confidence interval, ECOG PS: Eastern Cooperative Oncology Group performance status

Table 5. Risk Factors for a Lack of Initial Treatment for Lung Cancer.

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	p value	Odd ratio	95% CI	p value
Depression						
Positive/negative	1.925	0.359-14.314	0.449			
Age(years)						
≥75/<75	2.355	0.416-13.342	0.316			
Sex						
Female/male	1.177	0.157-6.361	0.856			
Clinical stage						
Inoperable IIIA-IV/I-operable IIIA	6.064	0.935-118.259	0.060			
ECOG PS						
≥2/0-1	2.111	0.104-15.146	0.545			
Smoking history						
Positive/negative	1.547	0.217-30.915	0.691			
Symptoms						
Positive/negative			0.001			<0.001
Marital status						
Married/divorced, separated, or single	0.768	0.093-15.960	0.827			
Occupation						
Retired or unemployed/employed			0.008			0.005

CI: confidence interval, ECOG PS: Eastern Cooperative Oncology Group performance status

Comparison of the clinical data of patients with and without the induction of treatment

Among 110 lung cancer patients, 104 (94.5%) were prescribed initial treatment, while 6 (5.5%) received the best supportive care (BSC). We compared the clinical data of patients with and without the induction of treatment (Table 4). According to the chi-squared test or Wilcoxon rank sum test, the proportions of patients with symptoms ($p=0.004$)

and those who were retired or unemployed ($p=0.029$) were significantly lower among patients with the induction of treatment than among those without. The results of the logistic regression analyses of the risk factors for a lack of initial treatment for lung cancer are shown in Table 5. The univariate and multivariate analyses revealed that the same 2 factors identified above (positive symptoms and lack of employment) were significant risk factors. On the other hand, depression was not a risk factor for the absence of initial

treatment induction for lung cancer.

Discussion

To the best of our knowledge, this is the first study to investigate the patient characteristics that are possible risk factors for depression before the diagnosis of lung cancer using a multivariate analysis. Our data showed that a poor PS was an independent risk factor. However, depression was not associated with the initial treatment induction rate in lung cancer patients.

A poor PS was also found to be a risk factor for depression in patients diagnosed with lung cancer in previous studies. Furthermore, advanced stage, female sex, and cancer pain have also been reported to be risk factors for depression (4, 5, 15). Moreover, a poor PS, presence of metastasis, and history of mental disorder have been reported as risk factors for depression, specifically before the diagnosis of lung cancer in a single study, which used a univariate analysis (8); our study was consistent with its findings in that a poor PS and advanced stage were risk factors for depression in the univariate analysis. However, in the multivariate analysis a poor PS was the only independent risk factor for depression before the diagnosis of lung cancer. Based on these results, patients with a poor PS should be screened for depression before the diagnosis of lung cancer.

That a poor PS is an independent risk factor for depression before the diagnosis of lung cancer may be attributable to the fact that physical symptoms such as a poor PS are known to be related to depression in cancer patients (5, 8, 15). In addition, the serum concentration levels of inflammatory cytokines such as interleukin-6 and tumor necrosis factor- α , which worsens the PS in cancer patients, are reportedly higher in patients with advanced lung cancer than in those with early-stage disease (24). These cytokines not only worsen the PS but can also exacerbate depression in cancer patients (25, 26). Thus, these could be the reasons why a poor PS was an independent risk factor for depression in the present study.

Previous studies revealed that before the diagnosis of breast cancer, patients with depression had low standard treatment induction rate (16, 17). However, in our study, depression before the diagnosis of lung cancer was not associated with the initial standard treatment induction rate in lung cancer patients. This discrepancy may have been caused by the variations in the definition of depression among investigators. In studies related to breast cancer, the subjects included patients who were previously diagnosed with depression and who had received treatment for it. On the other hand, the subjects in our study were patients who were only currently diagnosed with depression using the QIDS-SR, and who had not yet received treatment. Another reason for the discrepancy is that, in breast cancer studies, the number of subjects and the proportion of women (female sex is itself a risk factor for depression) were higher in comparison to our study.

Our study was performed at a single institution and included a small number of subjects, which was a limitation of our study. In particular, depression before the diagnosis did not affect the initial standard treatment induction rate in the present study. The small number of study subjects might have influenced this result. Thus, further multicenter studies of large cohorts are required to verify our findings. Additionally, the change in depression scores after appropriate treatment was not investigated in the present study. Further studies are also needed to examine this issue.

In conclusion, this study showed that a proportion of lung cancer patients are complicated with depression before the diagnosis of lung cancer. A poor PS is an independent risk factor for such depression. Thus, physicians should evaluate whether lung cancer patients with a poor PS are experiencing depression before their diagnosis.

The authors state that they have no Conflict of Interest (COI).

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