Depression and survival in patients with non-small cell lung cancer after curative resection: a preliminary study

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Psychological depression is thought to be a predictor of poor survival among cancer patients. The objective of the present study was to investigate the association between depression and survival in surgically treated Japanese patients with non-small cell lung cancer (NSCLC). From June 1996 through April 1999, a total of 229 patients with postoperative lung cancer were enrolled. Three months after the patients' surgery, the Structured Clinical Interview for DSM-III-R (SCID) and the Profile of Mood States (POMS) were used to assess the patient for depression, based on the interviewers' rating and a self-report, respectively. The follow-up period consisted of a total of 14 342 person-months (median = 69 months). As of January 2004, 55 deaths had occurred within the follow-up period. A Cox regression was used to estimate the hazard ratio (HR) of mortality adjusting for age, sex, smoking status, occasion of diagnosis, pathological stage and preoperative percentage forced expiratory volume in 1 s. The depression-dejection subscale on the POMS was divided into three score levels. The multivariate HR of survival for individuals with depression, as diagnosed by the SCID, was 2.2 (95% confidence interval 0.8–6.0) (*P*-value = 0.14), compared with individuals without depression. The multivariate HR of survival for subjects in the highest level of the POMS Depression–Dejection subscale was 1.4 (0.7–2.6), compared with in the lowest level (trend *P*-value = 0.0502). This prospective cohort study in Japan does not support the hypothesis that depression is associated with survival among NSCLC patients after curative resection, but further analysis involving a long-term follow-up period is needed. (*Cancer Sci* 2006; 97: 199–205)

Lung cancer is the most common form of cancer and the most common cause of cancer-related death in the world.[1,2] In Japan, lung cancer is the leading cause of death from cancer among men and women, and the incidence of lung cancer has been increasing in recent years. In 2003, the number of lung cancer deaths reached 41 615 (22% of all cancer-related deaths) in men and 15 086 deaths (12% of all cancer-related deaths) in women.[3] For prognosis and for therapeutic strategies, differentiating between non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) is important; these cancers account for nearly 80% and 20% of all lung cancers, respectively.[4] Although radical surgery is the primary treatment for early NSCLC, the long-term survival of patients who undergo surgery alone is disappointing, with estimated 5-year survival rates ranging from 67% for those with pathological stage IA disease to 39% for those with pathological stage IIB disease.[5] Determining progression in patients with NSCLC is difficult, partly because of the marked clinical heterogeneity of patients with this disease.[5] In earlier reports, various individual characteristics such as age, sex, pathological stage, performance status (PS), comorbidity, molecular biological markers, marital status and smoking status were shown to play a role in survival from lung cancer.[6,7] Further clarification of the factors contributing to survival from lung cancer is needed.

Depression has also been speculated to be a predictor of survival among lung cancer patients.[6] In most of the earlier studies on the association between depression and cancer survival, potential intermediary factors, like endocrinological or immunological pathways, were assumed to influence the association.[8–10] To date, 11 prospective studies have reported a statistically significant association between depression and survival in patients with various kinds of cancer, not only lung cancer.[11–21] Of the four prospective studies focusing on lung cancer patients,[15,22–24] one found a statistically significant association between higher depression scores and an increased risk of mortality from lung cancer.[15] The other three studies did not find any significant association between depression and survival from lung cancer.[22–24] The majority of these studies had some methodological limitations, including the failure to control sufficiently for potential confounding variables such as comorbidity, respiratory function, smoking status and social support;[15,22–24] the use of a self-reported questionnaire on depression and the absence of a structured clinical interview in some of these studies were further limitations.[15,22,24]

To further examine the association between depression and survival in patients with lung cancer, we conducted a prospective cohort study in Japan. This study assessed depression using both a structured clinical interview and a self-reported questionnaire at 3 months after complete resection, and focused on patients with NSCLC.

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Materials and Methods

Study cohort

The design of the present study has been reported in detail elsewhere.[25,26] Briefly, we invited patients with resectable NSCLC who were scheduled for treatment in the Thoracic Oncology Division of the National Cancer Center Hospital East, Kashiwa, Japan, to participate in the study. The eligibility criteria were: an age of 18 years or older; an awareness of the diagnosis of cancer; the ability to speak Japanese; a predetermined standard surgical procedure (lobectomy or pneumonectomy with mediastinal lymph node dissection); no evidence of brain tumor on computed tomography or magnetic resonance images of the head; no history of or current use of chemotherapy, immunotherapy or radiation therapy; no active concomitant cancer; curative resection based on pathology reports indicating an International Union Against Cancer disease stage of pT1 to pT3, pN0/1 or pM0;[27] and no other medical conditions.

As a result, a total of 303 patients with NSCLC were enrolled in the study between June 1996 and April 1999. The study protocol was approved by the institutional review board of the National Cancer Center, Tokyo, Japan. Each patient was fully informed as to the purpose of the study before written consent was obtained.

Exposure data

Various demographic and clinical variables were noted before surgery (baseline) or 3 months after surgery, including age, sex, weight, height, marital status, educational period, employment, smoking status, presence of confidants, occasion leading to diagnosis, pathological stage, histology type, type of surgery, PS, pain, dyspnea, percentage vital capacity (VC), percentage forced expiratory volume in 1 s (FEV 1.0%), comorbidity (hypertension, myocardial infarction, angina pectoris, diabetes mellitus, renal diseases and liver diseases) and albumin level. With regard to smoking status, 'continued smokers' were defined as those who continued smoking at 3 months after surgery, while 'quit smokers' were defined as those who had stopped smoking within the previous year and 'ex-smokers' were defined as those who had quit smoking 1 or more years before surgery. Pain and dyspnea were graded on a four-point verbal scale: 0, absent; 1, mild; 2, moderate; or 3, severe. A psychiatric interview and a self-reported psychological questionnaire were used to assess the patients for depression 3 months after surgery.

Structured Clinical Interviews for DSM-III-R-Depression

A trained psychiatrist assessed the current depression of the patients using Structured Clinical Interviews for Structured Clinical Interviews for DSM-III-R (SCID) depression structured interviews.[26,28] The presence or absence of the following nine items at the time of the interview was noted, and the total number of items present was regarded as the number of depressive episode items: (1) depressive mood; (2) diminished interest or pleasure; (3) change in body weight or appetite; (4) insomnia or hypersomnia; (5) psychomotor agitation or retardation; (6) fatigue or loss of energy; (7) feelings of worthlessness or guilt; (8) loss of concentration or indecisiveness; and (9) suicidal thoughts. The diagnosis of depression was made according to the criteria for major and minor depression. Major depression was diagnosed when five or more items, including either depressive mood or diminished interest or pleasure, were present; minor depression was diagnosed when two to four items, including depressive mood or diminished interest or pleasure, were present. The present analysis grouped patients with current minor depression and current major depression together.

As expected, determining whether somatic symptoms, like appetite loss, insomnia and fatigue, were attributable to depression or the surgical treatment was difficult. Four approaches have been used to diagnose depression in medically ill patients: (1) exclude somatic symptoms (exclusive); (2) substitute psychological symptoms for somatic symptoms (substitutive); (3) count somatic symptoms toward a depression diagnosis unless the symptom is clearly and fully accounted for by a general medical condition (etiological); and (4) include somatic symptoms (inclusive).[29] Because the rater must speculate as to the cause of individual symptoms, the etiological approach may be less reliable than the exclusive, substitutive and inclusive approaches. We elected to use an inclusive diagnostic approach (to prevent the underdiagnosis of depression), which is considered to be the most important clinical approach, although this approach may overestimate depression in medically ill patients. The reliability of the interview ratings was determined by having a second rater attend 30 interviews at random. The inter-rater agreement (Kappa) value for the diagnosis of depression was 0.78. The ratings for each of the nine individual items were also reliable, with Kappa values ranging from 0.65 to 1.00.

Profile of Mood States

The Profile Of Mood States (POMS) was developed to assess transient distinct mood states.[30,31] The original form of the measure consisted of 65 adjectives that were rated on a five-point scale from not at all to extremely. Developed on the basis of a series of factor analytical studies,[30] six factor-based subscales were derived: tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia, vigor-activity and confusion-bewilderment. The validity and reliability of the Japanese version of the POMS have been confirmed.[31] In the present study, only the depression-dejection subscale was used as a measure of depression.

Follow up

Survival of the subjects was followed from June 1996 through to January 2004. Out of the 303 subjects (189 men and 114 women) who underwent surgery between June 1996 and April 1999 and who were registered for the semistructured interviews, curative resection was confirmed by the final pathological report of the disease stage in 262 (86.5%) subjects. At the time of the 3-month postsurgery interview, three patients could not be contacted and 28 refused to participate in the study because of the psychological or physical burden, or other reasons; two patients had died. As a result, a total of 229 (138 men and 91 women) patients were included in the final analysis. We observed little difference between the patients who initially participated in the study ($n = 262$) and those whose data were

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analyzed ($n = 229$). Specially, the mean ages were 62.7 years in the initial group and 62.4 years in the analyzed group, and the proportion of men was 59.9% in the initial group and 60.3% in the analyzed group. Together, these findings indicate that the analyzed subjects were representative of the total patients in the study.

The person-months of follow-up were counted for each subject from the date of study enrollment until the date of death or the end of the study period (January 2004), whichever occurred first. The follow-up period consisted of a total of 14 342 person-months (median = 69 months, range = 3–89 months). A total of two subjects (0.9% of the analyzed cohort) were lost to follow up during the study period. During the follow-up period, 55 deaths from all causes were identified.

Statistical analysis

Subjects were excluded from the analysis if they did not answer one of the questions in the structured interview or the self-administered questionnaires; consequently, SCID data from 229 subjects and POMS data from 226 subjects were analyzed. The scores of the POMS depression-dejection subscale were divided into three approximately equal score levels based on the scores of all of the subjects. The hazard ratio (HR) and 95% confidence intervals (CI) were computed as the death rate among subjects with high or intermediate scores (or the presence of SCID depression) divided by the death rate among subjects with low scores (or the absence of SCID depression). We used the SAS PHREG procedure on SAS version 8.2 statistical software package (Cary, NC, USA) to evaluate Cox proportional-hazard regression to adjust for potentially confounding variables.[32] *P*-values for testing statistical significance of linear trends were calculated by treating the scores of the depression-dejection score as a continuous variable. A *P*-value of less than 0.05 was considered statistically significant. All *P*-values were two-tailed.

First, we analyzed the unadjusted HR of survival in patients with surgically treated lung cancer according to various demographic and medical variables; then, we carried out a multivariate analysis to adjust for potential confounders with a statistically significant effect on survival. In addition to sex and age in years at the time of cancer diagnosis (10-year age groups), we considered the following variables as *a priori* confounders: marital status (married or unmarried), education (college/university or higher or high school or less), employment (full time/part time or other), smoking status (never smokers, past smokers, quit smokers or continued smokers),[26] presence of confidant (presence or absence),[33,34] occasion of diagnosis (mass screening and health checkup, subjective symptoms, follow up for other diseases or unknown), pathological stage (IA, IB, IIA, IIB or IIIA), histological type (adenocarcinoma, squamous cell carcinoma, large cell carcinoma or other), type of surgery (lobectomy or pneumonectomy), pre- and postoperative PS as defined by the Eastern Cooperative Oncology Group (0 or higher),[35] pain (none to mild or moderate to severe),[26] dyspnea (none to mild or moderate to severe),[26] preoperative percentage VC (<80 or ≥80), preoperative FEV 1.0% (<70 or ≥70), comorbidity (combined with hypertension, myocardial infarction, angina pectoris, diabetes mellitus, renal diseases or liver diseases), and albumin level.

For the survival estimates, we analyzed both all-causes of death (55 cases) and total cancer deaths (41 cases) or lung diseases deaths (40 cases).

Results

We first compared the characteristics of subjects according to the SCID depression criteria or POMS depression-dejection subscale using χ^2 analysis to compare two categorical variables. The percentage of subjects with depression according to the SCID depression criteria was 5.7% ($n = 13$). Subjects with depression were more likely to have a poor PS at 3 months after surgery (*P*-value = 0.030) and moderate to severe pain (*P*-value = 0.007) (Table 1). The subjects who scored highly on the POMS Depression-Dejection subscale were more likely to have confidants (*P*-value = 0.046). The other demographic and medical variables were not associated with depression.

In the univariate Cox proportional hazard regression analyses, six demographic or clinical variables – age (70 years or older), sex (male), smoking status (past smokers or quit smokers), occasion of cancer diagnosis (follow up for other diseases), pathological stage (IB, IIA, IIB, or IIIA), and preoperative FEV 1.0% (<70), were significantly associated with increased HR for lung cancer survival compared with each referent category. Therefore, the multivariate analyses used these variables to evaluate their effect on survival (Table 2).

Table 3 shows the HR for lung cancer survival according to the depression diagnosis as assessed by the SCID. The HR for mortality risks in lung cancer patients with depression tended to be high but the trend was not significant: the unadjusted HR was 2.0 (95% CI = 0.8–5.0) (*P*-value = 0.14), compared with patients without depression. After controlling for age, sex, smoking status, occasion of diagnosis, pathological stage and preoperative FEV 1.0%, the effect of depression on survival was basically unchanged: the multivariable adjusted HR was 2.2 (0.8–6.0) (*P*-value = 0.14). The multivariable HR of survival for individuals in the highest level of the POMS depression-dejection subscale was 1.4 (0.7–2.6), compared with individuals in the lowest level (trend *P*-value = 0.0502). We further adjusted the analysis to include PS at 3 months after surgery, pain and the presence of confidants in addition to the previous multivariable analysis (see Table 2). As a result, our observations were quite similar and replicated (data not shown).

For the survival estimates, we also used the total cancer deaths (41 cases) or lung disease deaths (40 cases) as endpoints. No significant associations between depression (SCID depression or POMS depression-dejection) and the risk of cancer mortality or the risk of lung disease mortality were observed (data not shown).

Discussion

The data obtained in the present prospective cohort study in Japan do not support the hypothesis that depression is associated with survival among NSCLC patients after curative resection. Our study had several methodological advantages compared with previous studies on depression and survival in patients with lung cancer. First, we assessed

Table 1. Demographic and medical characteristics of study subjects according to depression: Structured Clinical Interview for DSM-III-R (SCID) depression and Profile of Mood States (POMS) depression-dejection

Characteristics	SCID depression		*P*-value	POMS depression-dejection			*P*-value
	Absence	Presence		≤2	3–6	≥7	
No. subjects	216	13		80	69	77	
Demographic characteristics							
Age at time of cancer diagnosis (%)			0.94				0.99
≤59 years	35	39		34	36	36	
60–69 years	35	31		38	33	35	
≥70 years	30	31		29	30	29	
Sex (%)			0.92				0.56
Male	60	62		64	62	56	
Female	40	39		36	38	44	
Marital status (%)			0.62				0.34
Married	82	77		84	87	78	
Unmarried	18	23		16	13	22	
Education (%)			0.75				0.54
College/university or higher	19	15		23	19	16	
High school or less	81	85		78	81	84	
Employment, full-time or part-time (%)			0.60				0.94
No	54	62		53	55	55	
Yes	46	39		48	45	46	
Smoking status (%)			0.59				0.33
Never smokers	36	39		33	32	42	
Past smokers	24	15		23	33	17	
Quit smokers	33	46		39	28	35	
Continued smokers	7	0		6	7	7	
Presence of confidants (%)			0.39				0.046
Absent	14	23		19	19	7	
Present	86	77		81	81	94	
Medical characteristics							
Method of diagnosis (%)			0.59				0.98
Mass screening or health checkup	61	31		20	22	18	
Subjective symptoms	19	62		63	59	60	
Follow up for other diseases	18	8		16	16	20	
Unknown	2	0		1	3	3	
Pathological stage[†](%)			0.74				1.00
IA	51	46		51	49	52	
IB	26	15		25	29	23	
IIA	5	8		5	4	5	
IIB	14	23		15	15	14	
IIIA	4	8		4	3	5	
Histology type (%)			0.53				0.44
Adenocarcinoma	68	85		64	67	74	
Squamous cell carcinoma	21	15		28	20	14	
Large cell carcinoma	4	0		4	6	3	
Other	7	0		5	7	9	
Type of surgery (%)			0.45				0.25
Lobectomy	96	100		98	93	97	
Pneumonectomy	4	0		3	7	3	
Pre-operative performance status[‡](%)			0.19				0.71
0	71	54		70	73	66	
1	29	46		30	28	34	
Performance status[‡] (%)			0.030				0.88
0	38	8		38	36	34	
1/2	63	92		63	64	66	
Pain (%)			0.007				0.95
None-mild	73	39		73	71	70	
Moderate-severe	27	62		28	29	30	
Dyspnea (%)			0.82				0.61
None-mild	72	69		74	74	68	
Moderate-severe	28	31		26	26	33	
Albumin (%)			0.51				0.64
≥3.5 g/100 mL	97	100		96	99	96	
<3.5 g/100 mL	3	0		4	2	4	
Pre-operative percentage VC (%)			0.30				0.29
≥80	93	85		95	93	88	
<80	7	15		5	7	12	
Pre-operative FEV 1.0% (%)			0.56				0.47
≥70	78	85		74	81	81	
<70	22	15		26	19	20	
Co-morbidity[§] (%)			0.95				0.88
Absent	61	62		61	62	58	
Present	39	39		39	38	42	

[†]Defined by a tumor nodule metastasis classification: International Union Against Cancer. [‡]Defined by Eastern Cooperative Onology Group. [§]Combined with hypertension, myocardiac infarction, angina pectoris, diabetes mellitus, renal diseases or liver diseases. FEV 1.0%, percentage forced expiratory volume in 1 s; VC, percentage vital capacity.

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Table 2. Unadjusted hazard ratios (HR) for death from all causes among patients with non-small cell lung cancer according to various demographic and medical variables

Characteristics	No. subjects	Median survival months (range)	No. cases	Univariate analysis	
				HR (95% CI)[†]	*P*-value
Demographic characteristics					
Age at time of cancer diagnosis					
≤59 years	80	70 (6–89)	11	1.0 (referent)	
60–69 years	80	67 (3–88)	21	2.1 (1.0–4.3)	0.051
≥70 years	69	68 (4–89)	23	2.6 (1.3–5.4)	0.008
Sex					
Male	138	67 (3–89)	43	1.0 (referent)	
Female	91	70 (7–89)	12	0.4 (0.2–0.7)	0.004
Marital status					
Married	188	68 (3–89)	48	1.0 (referent)	
Unmarried	41	71 (4–89)	7	0.6 (0.3–1.4)	0.28
Education					
College/university or higher	43	68 (8–86)	7	1.0 (referent)	
High school or less	186	69 (3–89)	48	1.6 (0.7–3.6)	0.30
Employment, full time or part time					
No	125	67 (6–89)	33	1.0 (referent)	
Yes	104	69 (3–89)	22	0.7 (0.4–1.3)	0.25
Smoking status					
Never smokers	82	70 (8–89)	9	1.0 (referent)	
Past smokers	54	67 (8–88)	18	3.2 (1.5–7.3)	0.004
Quit smokers	78	64 (3–89)	24	3.1 (1.5–6.8)	0.003
Continued smokers	15	69 (6–89)	4	2.6 (0.8–8.4)	0.11
Presence of confidants					
Absent	34	62 (16–89)	7	1.0 (referent)	
Present	195	69 (3–89)	48	1.2 (0.5–2.6)	0.70
Medical characteristics					
Methods of diagnosis					
Mass screening or health checkup	139	70 (4–89)	27	1.0 (referent)	
Subjective symptoms	45	67 (3–87)	9	1.2 (0.5–2.5)	0.69
Follow up for other diseases	40	62 (7–88)	18	2.9 (1.6–5.6)	<0.001
Unknown	5	67 (51–88)	1	0.9 (0.1–6.9)	0.95
Pathological stage[‡]					
IA	117	72 (16–89)	17	1.0 (referent)	
IB	58	64 (7–89)	13	1.8 (0.9–3.6)	0.099
IIA	11	62 (16–75)	5	4.2 (1.5–11.4)	0.005
IIB	34	64 (6–88)	15	3.9 (2.0–7.9)	<0.001
IIIA	9	39 (3–72)	5	7.1 (2.6–19.3)	<0.001
Histology type					
Adenocarcinoma	157	69 (4–89)	38	1.0 (referent)	
Squamous cell carcinoma	47	65 (7–88)	13	1.1 (0.6–2.2)	0.69
Large cell carcinoma	9	60 (3–71)	3	1.7 (0.5–5.6)	0.38
Other	16	69 (14–89)	1	0.2 (0.0–1.8)	0.16
Type of surgery					
Lobectomy	220	69 (3–89)	54	1.0 (referent)	
Pneumonectomy	9	68 (52–85)	1	0.4 (0.1–3.0)	0.39
Pre-operative performance status[§]					
0	160	70 (4–89)	36	1.0 (referent)	
1	69	66 (3–87)	19	1.3 (0.8–2.3)	0.30
Performance status[§]					
0	82	69 (3–88)	18	1.0 (referent)	
1/2	147	69 (4–89)	37	1.2 (0.7–2.1)	0.51
Pain					
None-mild	163	69 (4–89)	38	1.0 (referent)	
Moderate-severe	66	66 (3–89)	17	1.2 (0.7–2.2)	0.47
Dyspnea					
None-mild	165	69 (4–89)	40	1.0 (referent)	
Moderate-severe	64	68 (3–89)	15	0.7 (0.3–1.7)	0.38
Albumin					
≥3.5	211	69 (3–89)	52	1.0 (referent)	
<3.5	7	63 (48–73)	3	2.0 (0.6–6.4)	0.25
Pre-operative percentage VC					
≥80	211	69 (3–89)	49	1.0 (referent)	
<80	18	68 (14–86)	6	1.5 (0.7–3.6)	0.33
Pre-operative FEV 1.0%					
≥70	179	69 (3–89)	36	1.0 (referent)	
<70	50	62 (6–87)	19	2.1 (1.2–3.7)	0.008
Co-morbidity[¶]					
Absent	139	69 (3–89)	31	1.0 (referent)	
Present	90	67 (4–87)	24	1.3 (0.8–2.2)	0.37

[†]All HR are given with 95% confidence intervals (CI) in parentheses. [‡]Defined by a tumor nodule metastasis classification: International Union Against Cancer. [§]Defined by Eastern Cooperative Onology Group. [¶]Combined with hypertension, myocardiac infarction, angina pectoris, diabetes mellitus, renal diseases or liver diseases. FEV 1.0%, percentage forced expiratory volume in 1 s; VC, percentage vital capacity.

Table 3. Hazard ratios (HR) of cancer survival according to depression: Structured Clinical Interview for DSM-III-R (SCID) depression and Profile of Mood States (POMS) depression-dejection†

Characteristics	SCID depression		*P*-value	POMS depression-dejection			Trend *P*-value
	Absent	Present		≤2	3–6	≥7	
No. deaths/total	50/216	5/13		19/80	15/69	20/77	
Median survival in months (range)	69 (3–89)	66 (7–87)		69 (6–89)	69 (3–89)	67 (4–89)	
Unadjusted HR	1.0 (referent)	2.0 (0.8–5.0)	0.14	1.0	0.9 (0.5–1.8)	1.1 (0.6–2.1)	0.19
Multivariable adjusted HR	1.0 (referent)	2.2 (0.8–6.0)	0.14	1.0	1.0 (0.5–2.1)	1.4 (0.7–2.6)	0.0502

†Multivariable HR is adjusted for age in years at the time of cancer diagnosis (≤59, 60–69, ≥70), sex, smoking status (never smokers, past smokers, quit smokers or continued smokers), methods of diagnosis (mass screening or health checkup, subjective symptoms, follow up for other diseases or unknown), pathological stage (IA, IB, IIA, IIB or IIIA), and preoperative percentage forced expiratory volume in 1 s (≥70 or <70). All HR are given with 95% confidence intervals in parentheses.

depression using a structured clinical interview and a self-reported questionnaire. Second, our study considered potential confounding variables like comorbidity, respiratory function, smoking status and social support.

In our analyses, we examined whether physical states and lifestyle characteristics influenced the association between depression and cancer survival. Physical states (stage and preoperative FEV 1.0%) and lifestyle characteristics (smoking status) were significantly associated with survival in patients with lung cancer but were not associated with depression. We observed small differences in the point estimates of the HR depending on whether multivariate adjustments were made for physical states and lifestyle characteristics (Table 3). Thus, these factors probably had minimal interaction with the trend between depression and cancer survival seen in this study. However, this study focused on patients with early stage cancer, and the physical burden on these patients was thought to be smaller than that for patients with advanced cancer. The interaction of depression, physical burden and cancer survival should be examined among patients with advanced cancer in the future.

For previous studies examining the association between depression and cancer survival, several prognostic factors have been hypothesized to play a role in the possible association between depression and survival from cancer. Potential intermediaries include endocrinological or immunological pathways.[33–35] However, our findings suggest that depression in lung cancer patients might not play an important role in survival.

To date, four prospective studies regarding the association between depression and survival in patients with lung cancer have been reported.[15,22–24] Faller and Schmidt followed 59 patients with lung cancer (NSCLC and SCLC) stage III or IV for approximately 5 years (longest follow-up period) and documented 54 deaths. Depression was assessed before treatment, and no significant association was found.[22] Faller *et al*. followed 103 patients with lung cancer (NSCLC and SCLC) stage I or IV for 7–8 years and documented 92 deaths. Depression was assessed before treatment, and no significant association was found.[23] Cody *et al*. followed 209 patients with inoperable lung cancer (NSCLC and SCLC) for 8 weeks (the number of deaths was not shown). Depression was assessed before treatment, and no significant association was found.[24] Buccheri followed 133 patients with lung cancer (NSCLC and SCLC) stage I to IV for approximately 2 years (longest follow-up period) and documented 44 deaths. The details of the depression assessment and the cancer treatment were not clearly stated, but subjects with higher depression scores (self-rating depression scale) had an increased risk of mortality compared with the subjects with lower scores (P-value = 0.048).[15] Our findings cannot be simply compared with these earlier studies. Our study only examined patients with NSCLC, whereas the earlier studies selected patients with SCLC as well as NSCLC.[15,22–24] Furthermore, our study focused on postoperative lung cancer patients (pathological stage IA to IIIA). Therefore, our study differs from earlier studies with regard to the cancer stage, treatment plan and survival rate. Three of the previous studies assessed depression before cancer treatments, and depression was not associated with survival from lung cancer in those studies.[22–24] The results of depression assessments made before cancer treatment might not play an important role in survival from lung cancer. Hjerl *et al*. indicated that postoperative depression was associated with a significantly higher risk of mortality among early stage patients of breast caner but that preoperative depression was not associated with a higher risk.[19] However, in our findings, postoperative assessments of depression were not associated with cancer survival among patients with NSCLC. The reasons for this finding were not clear, but differences in physical status arising from cancer treatment may not be associated with depression, and may not influence survival.

Our study has several limitations. First, the number of subjects and deaths were relatively small (229 patients and 55 deaths). Although a significant association was not found between psychological depression and survival in the lung cancer patients, the analyses may not have had sufficient statistical power to detect associations between small increases or decreases in the risk of mortality; thus, further analysis involving a long-term follow-up period is needed. Second, at the time of the 3-month postsurgery interview (n = 262), three (1.1%) patients could not be contacted and 28 patients (10.7%) refused to participate because of the psychological or physical burden, or other reasons. The analyzed subjects may have had a better health status, with regard to psychological or physical burden, than the initial patient group, and the present results might underestimate the association between psychological variables and survival in patients with lung cancer. Third, we focused on depression only at 3 months after complete resection because the assessment of

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depression immediately after a complete resection can be confounded by the surgery, whereas the assessment of depression at a long interval after complete resection can be confounded by life events other than the lung cancer. Thus, we assessed depression at 3 months after complete resection to minimize these effects. Last, we focused on patients with postoperative (early stage) NSCLC, and considered about intervention of depression and to exclude the influence of physical burden (e.g. cancer treatment) on depression. The results for this patient group may not be generally applicable.

In conclusion, the data obtained in this prospective cohort study in Japan do not support the hypothesis that depression is associated with survival among NSCLC patients after curative resection. Further analysis involving a long-term follow-up period is needed, giving increased statistical power and a clearer result.

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