Table 4 Side effect profile of fluvoxamine

side-effect		N of comparisons	N of participants	RR	95% CI
Cardiovascular					
Hypotenion/bradycardia	TCA	8	930	0.50	0.27, 0.92
Hypertension/tachycardia	Milnacipran	3	241	0.42	0.19, 0.93
Dermatological					
Sweating	Paroxetine	1	60	0.30	0.09, 0.98
Gastrointestinal					
Constipation	TCA	14	1357	0.68	0.49, 0.94
Dry mouth	TCA	16	1427	0.47	0.36, 0.63
	Maprotiline	2	82	0.10	0.01, 0.89
	Moclobemide	2	191	4.30	1.10, 16.70
Nausea/vomiting	TCA	17	1496	1.94	1.52, 2.47
	Mianserin	2	125	6.80	1.55, 29.75
	Milnacipran	3	241	1.47	1.03, 2.08
	Mirtazapine	1	412	2.85	1.70, 4.79
Weight loss	TCA	4	226	2.25	1.11, 4.56
Neuropsychiatric					
Anxiety/agitation	Mirtazapine	1	412	0.19	0.05, 0.63
Somnolence/drowsiness	Mirtazapine	1	412	0.55	0.38, 0.81
Tremor	TCA	12	1247	0.62	0.44, 0.88
Dizziness/vertigo	TCA	13	1283	0.31	0.22, 0.44

RR, relative risk. RR < 1 favours fluvoxamine.

a large majority was sponsored by pharmaceutical company marketing fluvoxamine (Buchkowsky and Jewesson, 2004; Perlis, *et al.*, 2005) and set fluvoxamine as an investigational drug (Barbui, *et al.*, 2004). Comparability between fluvoxamine and TCAs in efficacy and tolerability may, therefore, not be unconditionally warranted; that is to say, the efficacy and tolerability of fluvoxamine over TCAs might be overestimated.

Finally, very few of the trials used standardised instruments in the reporting of side effects, and many of the side effects experienced by patients prescribed ADs may readily be confused with symptoms and signs of depression. Many trials reported the number of patients who experienced any unwanted signs and symptoms during trials, but some articles defined side effects strictly as experiences that appeared for the first time during the treatment period, or experiences that appeared between screen and baseline but increased severity during the treatment period. On the contrary, some trials did not report the side effect profile. It is obvious that the emphasis on detecting side effects differs between trials, and this alone may explain some of the observed differences.

However, the strengths of the current study lie in the comprehensiveness of the study search we undertook and the strict quality appraisal for any study to be included in the final pooling of the results. We also imputed response and remission outcomes by applying a threshold of the most conventional and prevalent depression severity scales such as HAM-D or MADRS with a validated statistical method, if they were not available in original trials. We believe that our methodology should be used in future systematic reviews as long as selective reporting of outcomes remains prevalent (Watanabe, *et al.*, in press).

In conclusion, there were no large differences between fluvoxamine and any other ADs in terms of efficacy and tolerability in the acute phase treatment of depression. However, there is evidence of differing side-effect profiles, especially when comparing gastrointestinal side effects between fluvoxamine and TCAs. The results of the study led us to conclude that clinicians should focus on practically or clinically relevant considerations including these differences in side-effect profiles.

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Symptom indicator of severity of depression in cancer patients: a comparison of the *DSM-IV* criteria with alternative diagnostic criteria

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Abstract

Objective: The objective of this study was to explore the performances of several diagnostic criteria items for judging the severity of major depression among cancer patients.

Method: Using modern item response theory, we examined the performances of the diagnostic criteria outlined by the *DSM-IV* and two sets of conceptual diagnostic criteria (the Endicott and the Cavanaugh criteria) in a series of 728 cancer patients who had been diagnosed with major depression using an inclusive approach.

Results: While all the *DSM-IV* diagnostic criteria, including feelings of worthlessness and suicidal ideation, had a low ability for discriminating the severity of depression, two proposed items (not participating in medical care and social withdrawal) appeared to be good markers of moderately severe major depressive disorder among cancer patients. In addition, the items "fearfulness or depressed appearance in face or body posture" and "brooding, self-pity or pessimism" may be good markers for mild major depressive disorders, while the item "cannot be cheered up, doesn't smile, no response to good news or funny situations" may be a good marker for severe major depressive disorder.

Conclusions: The findings of the present study suggest that alternative criteria may have utility in diagnosing depression severity in cancer patients.

Keywords: Cancer; Depression; Severity; Diagnosing; Antidepressant

1. Introduction

Major depression is among the most widely recognized psychiatric disorders in cancer patients [1]. It not only produces serious suffering [2] but also worsens quality of life [3], reduces adherence to anticancer treatments [4], can lead to suicide [5], is a psychological burden on the family [6] and prolongs hospitalization [7]. Thus, early detection and appropriate management of major depression in cancer patients are crucial. On the other hand, there are several issues surrounding the appropriate assessment of major depression in cancer patients.

First, diagnosing major depression in cancer patients itself has been challenging because the diagnostic criteria for major depression, as established in the *DSM-IV*, include a number of signs and "somatic symptoms" that frequently are

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Table 1
Suggested criteria for diagnosing major depression in medical patients

	DSM-IV (etiologic approach)	Modified *DSM-IV* (inclusive approach)	Cavanaugh criteria (exclusive approach)	Endicott criteria (substitutive approach)
Common parts	1. Dysphoric mood 2. Loss of interest or pleasure 3. Psychomotor agitation or retardation 4. Feelings of worthlessness, self-reproach or excessive or inappropriate guilt 5. Recurrent thoughts of death, suicidal ideation, wishes to be dead or suicidal attempt			
Suggested parts	6. Diminished ability to think or concentrate or indecisiveness	Same as the left	6. Diminished ability to think or concentrate or indecisiveness	6. Fearfulness or depressed appearance in face or body posture
	7. Weight loss or gain or a decrease in appetite		7. Not participating in medical care in spite of ability to do so, not progressing despite improving medical condition and/or in functioning at a lower level than the medical condition warrants	7. Social withdrawal or decreased talkativeness
	8. Insomnia or hypersomnia			8. Brooding, self-pity or pessimism
	9. Fatigue or loss of energy			9. Cannot be cheered up, doesn't smile, no response to good news or funny situations
Concept	Symptoms that are clearly and fully attributable to the general medical condition are excluded	Symptoms are counted regardless whether or not they might be attributable to cancer	Somatic symptoms are deleted from the diagnostic criteria	If the medical condition is likely to affect the specific symptoms (appetite/weight change, sleep, loss of energy/fatigue, diminished ability to think/concentrate), use the substitute symptoms

often attributable to the cancer itself and/or to anticancer treatments like chemotherapy and radiotherapy (e.g., appetite loss, weight loss, insomnia, fatigue, loss of energy and diminished ability to think or concentrate) [1]. Although the original *DSM-IV* diagnostic criteria exclude symptoms that are clearly and fully attributable to the general medical condition (etiologic approach), a differential diagnosis is often difficult or even impossible [8]. Some investigators, including our group, have attempted to assess the usefulness of several biological markers for diagnosing major depression in cancer patients, including measures of the hypothalamic–pituitary–adrenal axis (dexamethasone suppression test) [9], cortisol [10], the hypothalamic–pituitary–thyroid axis (TRH stimulation test) [9,11], serotonin-induced platelet calcium mobilization [12], IL-6 [10,13], and omega-3 fatty acid [14]; brain morphological differences in the hippocampus [15], amygdala [16] and prefrontal cortex [16]; and cerebral glucose metabolism [17]. However, none of these markers have proved to be definitive. Several alternative approaches have been proposed to resolve this diagnostic issue (Table 1) [18]; these approaches include inclusive (symptoms are counted whether or not they might be attributable to cancer) [19], substitutive [non-somatic symptoms are substituted with somatic symptoms (e.g., Endicott criteria) [20]] and exclusive [somatic symptoms are deleted from the diagnostic criteria (e.g., Cavanaugh criteria) [21]] approaches as well as an increased threshold approach (applying high symptom-severity thresholds for somatic symptoms) [22]. In addition, our previous study suggested that individual somatic symptoms differ in nature and that appetite-related symptoms and a diminished ability to think may be useful for diagnosing depression in cancer patients, whereas sleep disturbances and fatigue may not (modified inclusive approach) [23]. Another previous study suggested the usefulness of somatic symptoms when applying the *DSM-IV* depression criteria to physically ill patients, including those with diabetes, ischemic heart disease and chronic obstructive lung disease [24]. Although the inclusive approach is generally recommended for diagnosing major depression in physically ill patients (especially in a clinical setting), to avoid underestimating depression [18,25], this approach may lead to false-positive diagnoses of depression [26]. Thus, standard methods for the diagnosis of major depression are needed but have not yet been established [8,18,27,28].

Second is an issue regarding the assessment of depression severity, which is determined by considering the number and intensity of symptoms, including both non-somatic and somatic symptoms. As diagnosing depression in cancer patients is difficult, determining the severity of depression is also difficult. Regarding treatments for clinical depression in cancer patients, previous studies have demonstrated the effectiveness of antidepressants for major depression [29,30]. On the other hand, these studies failed to show the effectiveness of antidepressants in cancer patients with milder depression, including those with adjustment disorders [31,32]. These findings suggest that only cancer patients with severe depression benefit from antidepressant treatment [33]. In general psychiatric settings as well, antidepressants usually become a principal treatment when major depression is severe [34]. Thus, the severity of major depression should be a relevant indicator for treatment implementation in cancer patients, and assessment of the overall severity of depression is relevant

for selecting appropriate treatments, especially the administration of antidepressants.

Some previous studies investigated symptoms as indicators of severe depression and/or major depression in cancer patients and found that feelings of worthlessness and suicidal ideation were good indicators of severe depression [2,35]. However, our clinical experience and some previous studies suggest that these symptoms are not rare and not specific to depression in cancer patients [36,37]. Thus, understanding symptom indicators for severe depression would be helpful in clinical practice, especially when considering whether to administer antidepressants.

The objective of this study was to use modern item response theory (IRT) to explore the performances of the diagnostic criteria items for major depression as outlined by the *DSM-IV* and two previously proposed diagnostic criteria (the Endicott and the Cavanaugh criteria) for judging the severity of major depression among physically ill/cancer patients.

2. Materials and methods

All psychiatric consultations referred to the Psychiatry Division, National Cancer Center Hospital and Hospital East, Japan, between 1996 and 2003 were reviewed. A computerized database was used to identify cancer patients with major depression using the results of a structured clinical interview based on the *DSM-IV* criteria by trained psychiatrists. During this study period, a total of seven psychiatrists, including four faculty and three residents, interviewed the patients. The resident psychiatrists were provided with continuous education about diagnosis of depression among cancer patients by faculty psychiatrists. The database included demographic factors, medical factors such as performance status and pain and psychiatric diagnoses based on the *DSM-IV* criteria (with major depression diagnosed using the inclusive approach). Performance status, as defined by the Eastern Cooperative Oncology Group criteria, is an objective index of a patient's physical functioning, ranging from 0 (*no symptoms*) to 4 (*bedridden*). To assess pain, the psychiatrists directly asked the patients about their pain at the time of the first interview; each patient's pain was then categorized as "not at all", "a little", "tolerable" or "intolerable". In addition, one item proposed by Cavanaugh (not participating in medical care in spite of ability to do so, not progressing despite improving medical condition and/or in functioning at a lower level than the medical condition warrants) [21] and four items proposed by Endicott (fearfulness or depressed appearance in face or body posture; social withdrawal or decreased talkativeness; brooding, self-pity or pessimism; cannot be cheered up, doesn't smile, no response to good news or funny situations) [20] (Table 1) were also evaluated in cases diagnosed with major depression; these items were also included in the database. Because no precise definition and/or assessment guidelines for these symptoms exist, the psychiatrists carefully judged each symptom from a clinical perspective; in many cases, several items of information were gathered from the medical staff and the patients' family members to evaluate these symptoms as accurately as possible. When a criterion was assessed as absent or subthreshold, it was entered as absent (rated as 0) in the database; when assessed as present, it was entered as such (rated as 1). Only data from patients diagnosed as having major depression for whom complete information for each diagnostic item in both the Cavanaugh and the Endicott criteria was available were extracted from the database and analyzed in the current study.

Patient sheets completed by the psychiatrists were automatically read using a mark sheet reader and were stored in the database. Then, an anonymous data set that could not be linked to the patient's charts was produced in March 2004. Since this was a retrospective study using an anonymous data set obtained during routine clinical practice and that could not be used to identify individuals, informed consent and institutional review board approval were not required according to the ethics guideline for epidemiological studies developed by the Japanese Ministry of Labor, Health and Welfare (http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/ekigaku/0504sisin.html).

2.1. Statistical analysis

As mentioned above, we used IRT analyses to examine whether the meaning or significance of specific depressive symptoms differed. We considered all 14 items of the *DSM-IV* (9 items), Endicott (4 items) and Cavanaugh (1 item) criteria as items in an overall test for major depression.

The IRT assumes that a test or a scale measures a unidimensional latent trait. The latent trait is the construct that is expected to be measured by a test and therefore represents the severity of major depression in this study. The probability of the response "yes" is expressed in the form of a monotonically increasing function of the latent variable, which is called theta (θ). In this case, the greater the severity of major depression, the higher the probability of a positive response to a question asking about the diagnostic symptoms. The theta (θ) at which half of the sample answers yes (the diagnostic symptom is present) to a particular item is called the difficulty parameter of this item. The second parameter in the IRT model is known as the discrimination parameter. It indicates the slope of the item response curve at the difficulty parameter of the item. Hence, the higher the value of the discrimination parameter, the steeper the slope and the better the ability of the item to discriminate the responder's trait at or around a certain severity. The relation between the latent trait and the probability of a positive response for an item can be described by the item characteristics curve (ICC). The difficulty parameter represents the horizontal location of this curve, while the discrimination parameter represents the slope. Thus, the two parameters are used to describe the relationship between each symptom and the overall severity of major depression. For example, if a specific symptom was a less powerful

Table 2
Characteristics of referred cancer patients with major depression (N=728)

Age (years)	
Mean±S.D.	58±12
Median (range)	59 (17–95)
Sex, *n* (%)	
Male	329 (45)
Female	399 (55)
Marital status, *n* (%)	
Married	578 (79)
Unmarried	85 (12)
Widowed	57 (8)
Others	8 (1)
Years of education, *n* (%)	
<12	133 (18)
≥12	434 (60)
Unknown	161 (22)
Employment status, *n* (%)	
Full-time	228 (31)
Part-time	27 (4)
Housewife	257 (35)
Retired	112 (15)
Others	104 (14)
Setting, *n* (%)	
Inpatient	470 (65)
Outpatient	258 (35)
Cancer site, *n* (%)	
Lung	152 (21)
Breast	108 (15)
Stomach	68 (9)
Head and neck	68 (9)
Colon	61 (8)
Esophagus	53 (7)
Pancreas	43 (6)
Malignant lymphoma	26 (4)
Leukemia	19 (3)
Uterus	18 (3)
Others	112 (15)
Stage, *n* (%)	
Metastatic/Recurrent	425 (58)
Others	303 (42)
Performance status[a,b], *n* (%)	
0	139 (19)
1	238 (33)
2	153 (21)
3	133 (18)
4	62 (9)
Pain[b], *n* (%)	
Absent	271 (38)
Mild	190 (26)
Tolerable	187 (26)
Intolerable	71 (10)

[a] Performance status, as defined by the Eastern Cooperative Oncology Group criteria, is an objective index of a patient's physical functioning, ranging from 0 (*no symptoms*) to 4 (*bedridden*).
[b] Some data are missing.

indicator of depression in cancer patients, we would expect the ICC to have a shallower slope (i.e., a weaker correlation with overall depression severity) or a lower theta (i.e., a symptom that tends to occur at a lower level of depression).

To confirm that the IRT is, indeed, applicable, we assessed the dimensionality of the 14 combined *DSM-IV*, Cavanaugh and Endicott criteria using an exploratory factor analysis (the principal component analysis relied on tetrachoric correlations) by TESTFACT 4.0 software [38]. The two IRT parameters of difficulty and discrimination were also estimated using the marginal maximum likelihood calculated by the computer program BILOG MG 3 [39].

3. Results

3.1. Patient demographics and medical characteristics

A total of 5431 cancer patients were referred during the study period. Among these patients, 728 (12.8%) who were diagnosed as having major depression according to the inclusive criteria were extracted from the database. The patient characteristics are shown in Table 2. Lung cancer was the most common diagnosis, while breast cancer was the second most common diagnosis. More than half of the

Table 3
Discrimination and difficulty parameters for each diagnostic criterion of major depression

Diagnostic criterion (prevalence)	Difficulty[a]	Discrimination[b]
Dysphoric mood (95%)	−4.544	−0.406
Loss of interest or pleasure (85%)	−2.376	0.490
Weight loss or gain or a decrease in appetite (75%)	−2.891	0.235
Insomnia or hypersomnia (71%)	−2.534	0.220
Psychomotor agitation or retardation (75%)	−1.985	0.346
Fatigue or loss of energy (92%)	−3.448	0.456
Feelings of worthlessness, self-reproach or excessive or inappropriate guilt (53%)	−0.205	0.393
Diminished ability to think or concentrate or indecisiveness (88%)	−3.194	0.396
Recurrent thoughts of death, suicidal ideation, wishes to be dead or suicidal attempt (41%)	0.615	0.376
Not participating in medical care[c] (51%)	−0.053	0.997
Fearfulness or depressed appearance in face or body posture (83%)	−1.329	1.054
Social withdrawal or decreased talkativeness (45%)	0.176	1.031
Brooding, self-pity or pessimism (66%)	−0.756	0.639
Cannot be cheered up, doesn't smile, no response to good news or funny situations (16%)	1.521	0.905

[a] Difficulty parameter: The probability of the response "yes" is expressed in the form of a monotonically increasing function of the latent variable, which is called theta (θ). In this case, the greater the severity of major depression, the higher the probability of a positive response to a question asking about the diagnostic symptoms. The theta (θ) at which half of the sample answers yes (the diagnostic symptom is present) to a particular item is called the difficulty parameter of the item.
[b] Discrimination parameter: It indicates the slope of the item response curve at the difficulty parameter of the item. Hence, the higher the value of the discrimination parameter, the steeper the slope and the better the ability of the item to discriminate the responder's trait at or around a certain severity.
[c] Not participating in medical care in spite of ability to do so, not progressing despite improving medical condition and/or in functioning at a lower level than the medical condition warrants.

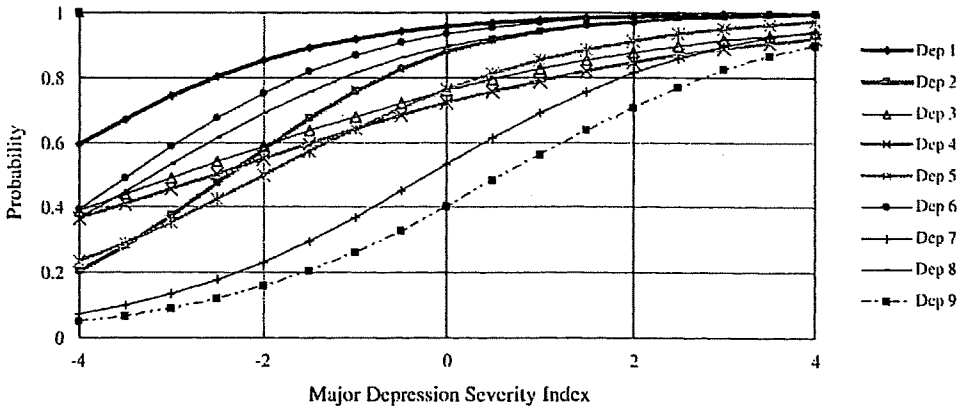

Fig. 1. ICCs of *DSM-IV* diagnostic criteria items for major depression in cancer patients. The curves show the probability that an individual symptom will be present as the overall severity of major depression increases. Depression severity is the trait measured by all items combined and is shown on a standardized scale (0=mean, 1 unit=1 S.D., −4=least severe depression, +4=most severe depression). Dep 1=dysphoric mood; Dep 2=loss of interest or pleasure; Dep 3=weight loss or gain or a decrease in appetite; Dep 4=insomnia or hypersomnia; Dep 5=psychomotor agitation or retardation; Dep 6=fatigue or loss of energy; Dep 7=feelings of worthlessness, self-reproach or excessive or inappropriate guilt; Dep 8=diminished ability to think or concentrate or indecisiveness; Dep 9=recurrent thoughts of death, suicidal ideation, wishes to be dead or suicidal attempt.

patients suffered from metastatic and/or recurrent cancer. More than 80% of the patients had some degree of decline in physical functioning (PS=1–4), and more than 60% of the patients had some degree of pain. Only 2 (0.27%) subjects did not disclose their cancer diagnosis.

3.2. Dimensionality

The exploratory factor analysis revealed that the first factor accounted for 26.1%, verifying that the data were sufficiently unidimensional for further IRT analysis.

3.3. Estimation of IRT parameters

The discrimination and difficulty parameters of the 14 diagnostic items are shown in Table 3. The ICCs provide visual summaries of the two parameters for each item (Figs. 1 and 2). Visual inspection of these ICCs reveals the following findings. Regarding the nine *DSM-IV* diagnostic criteria (Fig. 1), most of the items [except for feelings of worthlessness (Dep 7) and suicidal ideation (Dep 9)] had a high probability at a low level of major depression severity. Thus, these seven criteria have relatively low difficulty and discrimination parameters. Both feelings of worthlessness (Dep 7) and suicidal ideation (Dep 9) appeared to have moderate difficulty and low discrimination parameters. These criteria are often not reported when the severity of major depression is low and gradually start to be reported when the severity of major depression becomes moderate (around θ=0). The item proposed by Cavanaugh (not participating in medical care in spite of ability to do so, not progressing despite improving medical condition and/or in

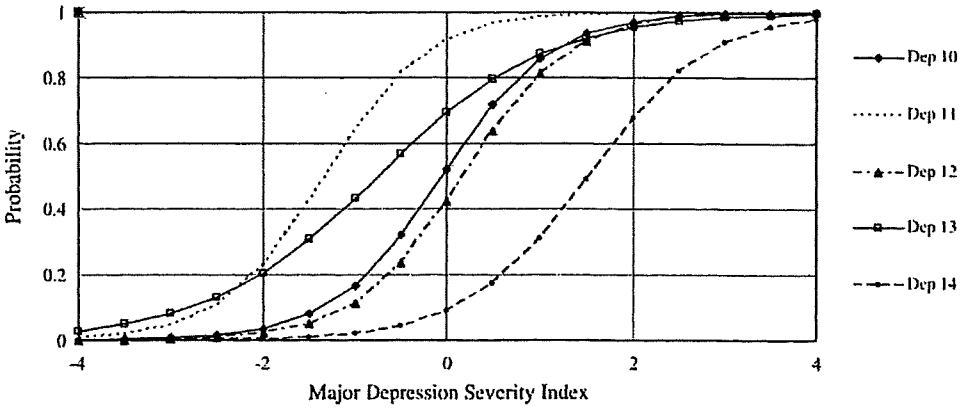

Fig. 2. ICCs of alternative diagnostic criteria items for major depression in cancer patients. The curves show the probability that an individual symptom will be present as the overall severity of major depression increases. Depression severity is the trait measured by all items combined and is shown on a standardized scale (0=mean, 1 unit=1 S.D., −4=least severe depression, +4=most severe depression). Dep 10=not participating in medical care; Dep 11=fearfulness or depressed appearance in face or body posture; Dep 12=social withdrawal or decreased talkativeness; Dep 13=brooding, self-pity or pessimism; Dep 14=cannot be cheered up, doesn't smile, no response to good news or funny situation.

functioning at a lower level than the medical condition warrants; Dep 10) had a moderate difficulty and a high discrimination parameter (Fig. 2). Among the four criteria proposed by Endicott, fearfulness or depressed appearance in face or body posture (Dep 11) and brooding, self-pity or pessimism (Dep 13) had relatively low difficulty and high discrimination parameters (Fig. 2). The item "cannot be cheered up, doesn't smile, no response to good news or funny situations (Dep 14)" had high difficulty and discrimination parameters. The item "social withdrawal or decreased talkativeness (Dep 12)" had a moderate difficulty and a high discrimination parameter.

4. Discussion

Our findings suggest that each individual symptom differs in nature and may occupy a specific position regarding the judgment of major depression severity in cancer patients.

As several previous studies have repeatedly indicated and/or suggested, the somatic symptoms (appetite loss, weight loss, insomnia, fatigue, loss of energy and diminished ability to think or concentrate) among the *DSM-IV* diagnostic criteria may not be useful for diagnosing and/or judging the severity of depression among cancer patients; this conclusion was supported by the results of our IRT analysis, which showed these symptoms to have low difficulty and low discrimination parameters. This finding is not surprising because these symptoms are well known to be common to both major depression and physical illness itself [35,40,41], and more than 80% of the subjects in the present study had some degree of physical function impairment. The IRT results also suggested that neither feelings of worthlessness nor suicidal ideation was a good indicator of the severity of major depression. Although several previous studies have suggested that among the operational diagnostic criteria items, including the Research Diagnostic Criteria and the *DSM-III* and/or *DSM-IV* criteria, the items "feelings of worthlessness" and "suicidal ideation" may be more useful than somatic items for evaluating the severity of depression [35,42]; our findings suggest that these items are not sufficiently useful for judging the severity of major depression in cancer patients. This outcome may be partly explained by the observation that these symptoms are also quite common symptoms of cancer itself. Several previous studies have demonstrated that cancer patients, especially advanced/terminally ill cancer patients, often suffer from the perception that they are a burden on others, and this perception is associated with a concern for others that can produce feelings of worthlessness, self-reproach or guilt [43–45]; these previous results may be related to the finding that the "worthlessness" item had a moderate difficulty and a low discrimination parameter. Thus, although the "worthlessness" item may be more useful than somatic items for diagnosing more severe depression among cancer patients, the usefulness of the "worthlessness" item seems to be limited when evaluating the severity of major depression in a consultation–liaison psychiatry setting. Similar findings regarding the "suicidal ideation" item have also been obtained in previous studies (e.g., suicidal ideation is quite common among cancer patients) [36,46–48], suggesting the limited usefulness of this item as a symptom indicator of severe major depression among cancer patients. As described above, the fact that the majority of the subjects in the current study were advanced cancer patients with a decline in physical functioning may support these findings. Thus, both feelings of worthlessness and suicidal ideation do not seem to be specific symptoms for evaluating the severity of major depression in cancer patients. These findings suggest that the current *DSM-IV* operational diagnostic approach may contain some weaknesses when applied to cancer patients.

On the other hand, the item proposed by Cavanaugh (not participating in medical care in spite of ability to do so, not progressing despite improving medical condition and/or in functioning at a lower level than the medical condition warrants) and one of the items proposed by Endicott (social withdrawal or decreased talkativeness) had moderate difficulty and high discrimination parameters in the IRT analysis and may be useful markers of the severity of major depression among cancer patients. These parameters appear to be good markers of moderately severe major depressive disorder in cancer patients (Table 4). In other words, when cancer patients have these symptoms, mental health professionals can presume that major depression may be at least moderately severe. As mentioned above, the inclusive approach is generally recommended for the diagnosis of major depression in physically ill patients in a clinical setting to avoid underdiagnosing depression. On the other hand, the inclusive approach often produces false-positive cases of major depression in whom the provision of standard psychiatric treatments [18], typically the administration of antidepressants, may not be necessary or may even be potentially harmful. Therefore, our findings suggest the

Table 4
Recommended items for evaluating severity of major depression in cancer patients

Severity of major depression	Recommended items for evaluation
Mild	Fearfulness or depressed appearance in face or body posture
	Brooding, self-pity or pessimism
Moderate	Not participating in medical care in spite of ability to do so, not progressing despite improving medical condition and/or in functioning at a lower level than the medical condition warrants
	Social withdrawal or decreased talkativeness
Severe	Cannot be cheered up, doesn't smile, no response to good news or funny situations

For example, the presence of the item "not participating in medical care in spite of ability to do so, not progressing despite improving medical condition and/or in functioning at a lower level than the medical condition warrants" can be a good marker of moderately severe major depressive disorder in cancer patients.

usefulness of a two-stepped diagnostic approach for evaluating moderately severe major depression among cancer patients, with the evaluation of these two items (not participating in medical care in spite of ability to do so, not progressing despite improving medical condition and/or in functioning at a lower level than the medical condition warrants, and social withdrawal or decreased talkativeness) after the application of the inclusive diagnostic approach. In addition, because the item "not participating in medical care in spite of ability to do so, not progressing despite improving medical condition and/or in functioning at a lower level than the medical condition warrants" is considered to be closely associated with the C criterion for major depression in the *DSM-IV* (the symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning), our findings suggest that an evaluation of the influence of the symptoms on social functioning is relevant for assessing the severity of major depression in cancer patients. Thus, when cancer patients are diagnosed with major depression using an inclusive approach, the evaluation of these symptoms may help clinicians to select appropriate treatment.

Each of the remaining three items proposed by Endicott also had unique characteristics for assessing the severity of major depression among cancer patients. The items "fearfulness or depressed appearance in face or body posture" and "brooding, self-pity or pessimism" had relatively low difficulty and high discrimination parameters and may be good markers for mild major depressive disorders among cancer patients (Table 4). However, because anxiety often coexists with depression in cancer patients and the predominance of anxiety may mask "fearfulness or depressed appearance in face or body posture", it may be potentially difficult to evaluate this item when a patient suffers from moderate to severe anxiety. Additionally, because judging body posture in bedbound, weak patients may also be difficult, the utility of the item "fearfulness or depressed appearance in face or body posture" may be limited in debilitated patients. On the other hand, the item "cannot be cheered up, doesn't smile, no response to good news or funny situations" had a high difficulty and a moderate discrimination parameter and may be a good marker for severe major depressive disorder in cancer patients (Table 4). These findings suggest that cancer patients with depression who exhibit the symptom "cannot be cheered up, doesn't smile, no response to good news or funny situations" may be appropriate candidates for the administration of antidepressants. Further study is needed to clarify which diagnostic criteria are most appropriate for diagnosing major depression among physically ill patients who may benefit from medical treatments.

Although it was not the principal purpose of our study, we would like to note that the current study demonstrated that all the items proposed by Cavanaugh and Endicott had higher discrimination parameters and were therefore better markers for evaluating the severity of major depression than any of the items included in the *DSM-IV* diagnostic criteria. These findings suggest the usefulness of alternative diagnostic approaches, rather than the *DSM-IV* approach, when diagnosing and/or assessing major depression among physically ill patients, especially among cancer patients, in a consultation–liaison psychiatry setting.

In conclusion, the findings of the present study suggest that alternative criteria may have utility in diagnosing depression severity in cancer patients. On the other hand, behavioral phenotypes (e.g., fearfulness or depressed appearance in face or body posture; brooding, self-pity or pessimism) need to be defined more rigorously in the future studies.

This preliminary retrospective study has several limitations. To determine the best approach to measuring depression severity, it would have been useful to compare the present results with an appropriate scale for depression severity, such as the Hamilton Depression Scale or the Beck Depression Inventory. However, such data were not available. Since only referred cancer patients diagnosed with major depression were used as subjects, our findings cannot be generalized to describe all cancer patients with depression. Another important problem is the inability to verify the reliability of the diagnostic interviews and the evaluations used to arrive at a diagnosis of major depression and to evaluate the proposed alternative diagnostic items. An evaluation manual regarding the alternative diagnostic criteria should be developed for future studies. In addition, the referred patient sample may have been influenced by a physician bias. Finally, because symptom profiles or the manifestation of symptoms of depression can be influenced by cultural differences [49,50], the obtained findings may not be generalized to patients in other countries.

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Psychosocial factors and survival after diagnosis of inoperable non-small cell lung cancer

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Abstract

***Objective*: Although several previous studies have investigated the association between psychosocial factors and the survival of lung cancer patients, most previous studies were flawed by severe methodological limitations. The purpose of the present study was to use a rigorous study design to investigate the association between relevant psychosocial factors and survival after a diagnosis of inoperable non-small cell lung cancer (NSCLC).**

***Methods*: The subjects were 122 consecutive newly diagnosed patients with inoperable NSCLC. Patients coping with cancer, psychological distress, clinical depression, and social support were evaluated after diagnosis but before treatment and 2 months later. After a 2-year follow-up period, 108 patients had died. The survival data were censored for the remaining 14 patients. The influence of psychosocial factors after diagnosis but before treatment on survival time was analyzed using a Cox regression, with adjustments for well-established (definite and/or possible) prognostic factors. The stability of the investigated psychosocial factors was also examined.**

***Results*: None of the examined psychosocial factors significantly predicted survival time among the patients with inoperable NSCLC. Among the biomedical factors that were examined, advanced clinical stage, a high serum lactate dehydrogenase level, and not receiving chemotherapy were independently associated with shorter survival periods. Most of the psychosocial factors exhibited a moderate to high stability.**

***Conclusions*: We found little convincing evidence that psychosocial factors after cancer diagnosis had a clinically relevant effect on the survival of inoperable patients with NSCLC.**

Keywords: coping; social support; survival; cancer; oncology

Introduction

There is much interest in the association between the mind and body, and this is not exceptional in oncology settings, possibly because cancer is a potentially life-threatening disease and is often accompanied by major psychological distress. Actually, many professionals and the lay public believe that psychosocial factors play a major role in cancer onset and its progression [1,2]. On the other hand, although several previous studies have investigated the effects of psychosocial characteristics (including personality, coping, general psychological distress, depression, and social support) on survival, the influence of psychosocial factors on the survival of cancer patients remains controversial [1,3–5].

Lung cancer is the most common type of cancer and the most common cause of cancer-related death in the world [6,7]. In Japan, lung cancer is the leading cause of death from cancer among men, and the incidence of lung cancer has been increasing in recent years [8]. In a study examining psychological distress and its relation to the site of cancer, primary lung cancer was strongly associated with psychological distress in cancer patients [9]. In addition, several previous studies have demonstrated that the highest prevalence of psychological distress was observed among patients with lung cancer [10,11]. Our previous study indicated that 19% of advanced lung cancer patients experienced diagnosable anxiety/depression between the time of diagnosis and initial treatment and that 35% of them continued to experience the same disorder for at least 6 months after diagnosis [12]. Thus, in general, psychological distress is highly prevalent among lung cancer patients; consequently, these psychosocial issues should not be neglected.

Several previous studies have investigated the association between lung cancer patient's psychosocial factors and survival. For example, Faller *et al.* reported a significant association between depressive coping/interviewer-rated emotional distress and a shorter survival period [13–15]. Nakahara *et al.* also demonstrated a significant association between mental state, as assessed using an egogram, and survival [16]. Other groups have reported significant associations between survival and depression [17], suicidal ideation [17], personality [18], psychosocial well-being [19], social support [19], and symptom distress [20], although some studies failed to clarify a significant influence of factors such as marital status [21], depression [15,22], social support [21], 24-h urinary cortisol level (used as an indicator of physiological or psychological stress) [23], self-reported psychological distress [13,14,20], and concerns [20]. On the other hand, most of these previous studies were flawed by severe methodological limitations, including a retrospective design [18,20], a short or unclear follow-up period (e.g. less than 1 year) [17,18], a small sample (e.g. less than 100 patients) [17,20], the lack of controls for well-established prognostic factors (especially because several biomedical factors have been identified as definite/possible prognostic factors among patients with non-small cell lung cancer (NSCLC) [24], and adjustments for these biomedical factors should be performed when evaluating other prognostic factors [25]) [13,14,18,20], and the assessment of variables after treatment (psychosocial factors should be evaluated at the same time as other biomedical factors, before treatment) [18,20]. In addition, none of the previous studies checked the stability of the investigated variables, although many psychosocial factors can change during the course of a patient's illness, and none of the studies simultaneously investigated a broad range of psychosocial factors, including diagnosable depression—known to be the most common psychiatric disorder, using a reliable measure, such as a structured clinical interview.

The purpose of the present study was to use a more rigorous study design to investigate the association between relevant psychosocial factors and patient survival after a diagnosis of inoperable NSCLC.

Patients and methods

Patients

The subjects were consecutive patients with NSCLC who had been newly diagnosed at the Thoracic Oncology Division, National Cancer Center Hospital East (NCCHE), Japan, between August 1996 and January 1998. Patients were included in the study if they met all of the following criteria: (1) histologically or cytologically confirmed NSCLC; (2) diagnosis of unresectable cancer (clinical stage unresectable IIIA, IIIB, or IV); (3) informed of their lung cancer diagnosis; (4) a performance status (PS) of between 0 and 2, according to the Eastern Cooperative Oncology Group criteria; (5) follow-up care at the Thoracic Oncology Division of the NCCHE; (6) 18 years of age or older; (7) not too ill to participate in an interview or complete questionnaires; (8) absence of brain metastasis, as confirmed using brain CT or MRI; (9) ability to provide written consent; (10) absence of cognitive impairment, such as delirium or dementia (if a subject was suspected of having a cognitive impairments, cognitive function was evaluated using the Mini Mental State Examination (MMS); only subjects with an MMS score of 24 or more were allowed to participate in the study [26]); (11) no history of previous anticancer treatment within 5 years; and (12) no active concomitant cancer.

This study was approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center of Japan and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each subject before enrollment into this study.

Assessment of psychosocial factors

We investigated each patient's coping with cancer, psychological distress, psychiatric disorders, and social support as potential psychosocial predictors of survival. These factors, other than the psychiatric disorders, were evaluated twice (after diagnosis but before treatment: baseline (T1), and 2 months after T1; T2) to check the stability of the factors. An assessment of psychiatric disorders was not conducted at T2 to avoid unnecessary increases of the patient's burden. The measures at baseline were investigated as potential prognostic factors.

Coping with cancer

Each patient's coping with having cancer was measured using the Japanese version of the Mental Adjustment to Cancer (MAC) scale [27]. The MAC scale consists of five subscales. Our previous study revealed that the Japanese version of the MAC scale was valid and reliable [27]. Among the subscales, we used fighting spirit and helplessness/hopelessness, which were shown to be potential prognostic factors in a previous study [28].

Psychological distress

Psychological distress was evaluated using the Profile of Mood States (POMS) [29]. The POMS is a 65-item self-rated scale for measuring mood

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disturbance. The POMS is a widely used, reliable measure of emotional distress that has been validated in cancer patients and demonstrated to be reliable for Japanese people [30]. The Total Mood Disturbance (TMD) scale of the POMS, which is the sum of the emotional state subscales, was used. A higher TMD indicates greater emotional distress.

Psychiatric disorders

A trained psychiatrist (T.A.) conducted a Structured Clinical Interview based on the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition–revised [31] to evaluate major depression and adjustment disorders in each patient. In addition, the patients were asked to complete the Hospital Anxiety and Depression scale (HADS) at baseline. The HADS is a 14-item self-reported questionnaire consisting of an anxiety and depression subscale; the total score can range from 0 to 42 [32]. Higher scores indicate more severe depression and anxiety. The Japanese version of the HADS was validated in a cancer population, and the optimal cutoff point for screening for adjustment disorder and major depressive disorder was 10/11 [33].

Social support

The patients' use of confidants (number of confidants and satisfaction with confidants) was used as an indicator of social support factors. This information was obtained in a structured interview, as described previously [34]. In the interview, the patients were asked the number of people they had confided in since being diagnosed with cancer and how satisfied they were with their interactions with these confidants.' When the patients had not confided in anyone, they were asked about their degree of satisfaction in not having done so. The patients' responses ranged from 1 to 7: 1, 'very dissatisfied'; 2, 'fairly dissatisfied'; 3, 'slightly dissatisfied'; 4, 'neither'; 5, 'somewhat satisfied'; 6, 'fairly satisfied'; and 7, 'very satisfied'.

Sociodemographic and biomedical factors

Sociodemographic factors (age, gender, marital status, education, household size, and employment status) were investigated using a structured interview at baseline. PS (assessed using the Eastern Cooperative Oncology Group criteria) was also investigated at baseline. In addition, the patient was asked about weight loss during the previous 6 months during the baseline interview. Blood laboratory tests (albumin level, hemoglobin level, leukocyte count, platelet count, and lactate dehydrogenase (LDH) level) were performed at the time of cancer diagnosis. (These biological factors were evaluated because they are definite/possible prognostic factors for NSCLC, as mentioned above.) Information on clinical stage and anticancer treatment were obtained from the patients' charts. Smoking status and alcohol consumption were not assessed in the study.

Statistical analysis

Survival was defined as the interval between the date of the pathological diagnosis of lung cancer and the date of death or the date of the last follow-up information for surviving patients. Survival was examined at 2 years after the study enrollment period. In addition to the psychosocial factors, sex, ECOG PS, disease stage, histology, albumin level, hemoglobin level, leukocyte count, platelet count, LDH level, weight loss, and the use of chemotherapy were analyzed. These factors include all the definite and/or possible prognostic factors of NSCLC other than biologic factors, such as oncogenes (e.g. ras, p53, etc.). All factors except for sex, treatment factors, clinical stage, and PS were treated as continuous variables (clinical stage and PS were treated as ordinal variables) [35]. The survival curves were estimated according to the Kaplan–Meier method. Because the Kaplan–Meier analysis indicated that there were a total of 108 events (deaths), up to approximately 11 covariates could be entered into the regression analysis for prognostic prediction [36]. We investigated the correlation among psychosocial factors; when a statistically significant correlation with a correlation coefficient of over 0.30 was observed, more clinically relevant factors were retained. Correlation coefficients of over 0.30 were obtained for the following pairs: helplessness/hopelessness and TMD, helplessness/hopelessness and HADS, and HADS and satisfaction with confidants. We prioritized TMD and satisfaction with confidants from a clinical point of view. Finally, a total of five psychosocial factors (fighting spirit, TMD, major depression, number of confidants, and satisfaction with confidants) were chosen for further investigation. Regarding biomedical factors, two definite prognostic factors (PS and disease stage) were compulsorily entered for adjustment [24]. As for other possibly relevant biomedical factors, we investigated the correlations among the factors and if a statistically significant correlation with a correlation coefficient over 0.30 was observed, more clinically relevant factors were retained. Correlation coefficients of over 0.30 were obtained for the following pairs: leukocyte count and platelet count, hemoglobin level and platelet count, hemoglobin level and albumin level, and platelet count and albumin level. We prioritized hemoglobin from clinical point of view. Finally, a total of six biomedical factors (PS, disease stage, histology, hemoglobin, serum LDH,

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and chemotherapy) were retained for further adjustment. Univariate and multivariate Cox proportional hazards regression models were used to determine the relationships between the investigated variables and survival. Biomedical and psychosocial variables that proved significant in the univariate analysis were simultaneously entered into the multivariate Cox regression, while PS and disease stage were compulsorily entered into the multivariate analysis regardless of the results of the univariate analysis. To explore the stability of the investigated psychosocial factors, except for the presence of the psychiatric diagnosis assessed by the psychiatric diagnostic interview, Pearson correlation coefficients or the concordance rate between T1 and T2 were investigated. A P value of less than 0.05 was adopted as the significance level in all of the statistical analyses, and all reported P values were two-tailed. All statistical procedures were conducted using the SPSS 10.0J version software for Windows (SPSS Inc., 2003).

Results

Characteristics of the participants

During the study entry period, 230 cases of unresectable NSCLC were newly diagnosed; 79 patients were found to be ineligible for enrollment in the study (brain metastasis, $n=44$; illness too severe, $n=16$; cognitive impairment, $n=8$; active concomitant cancer, $n=4$; not informed of the diagnosis, $n=3$; PS of 3 or 4, $n=3$; illiteracy, $n=1$). Among the remaining 151 eligible patients, 21 patients refused to participate in the study and 8 patients could not be contacted; thus, 122 patients ultimately participated. No significant differences in age, sex, marital status, employment, histology, or clinical stage were observed between the participants ($n=122$) and the non-participants ($n=21$); however, the non-participants had significantly lower PSs than the participants ($P=0.005$).

The patient characteristics are shown in Table 1. About half of the subjects were diagnosed as having stage IV lung cancer, and the overall median survival period was approximately 8.5 months. A total of six patients suffered from major depression. After a 2-year follow-up period, 108 patients had died. The survival data were censored for the remaining 14 patients.

A comparison of the survival of patients with various biomedical and psychosocial factors using a univariate analysis is shown in Table 2. Among the psychosocial factors, none of the investigated factors, including coping with cancer, psychological distress, psychiatric disorders, and social support, were significantly associated with the survival period. Among the biomedical factors, a higher serum LDH level and not receiving chemotherapy were significantly associated with shorter survival periods.

Table 1. Patient characteristics ($n=122$)

		No (%)
Age (years)	Mean±SD	62±9
	Median (range)	64.5 (40–82)
Sex	Male	90 (74)
Marital status	Married	107 (88)
Education	<10 y	62 (51)
Employment status	Full-time	34 (28)
	Part-time	5 (4)
	Housewife	15 (12)
	Retired	40 (33)
	Others	28 (23)
Household size	Living alone	8 (7)
Profile of Mood States (Total Mood Disturbance)	Mean±SD	34.3±33.3
	Median	27
Performance Status[a]	0	12 (10)
	1	104 (85)
	2	6 (5)
Histology	Adenocarcinoma	81 (64)
	Squamous cell	31 (25)
	Large cell	9 (7)
	Adenosquamous	1 (1)
Disease stage	III A	4 (3)
	III B	59 (48)
	IV	59 (48)
Survival (months)	Mean	11
	Median	8.6
	25 percentile	5.4
	75 percentile	15.2

[a]As defined by the Eastern Cooperative Oncology Group criteria.

Table 2. Comparison of the survival of patients with various biomedical and psychosocial factors—univariate Cox proportional regression analyses

Variable	Coefficient	SE	Hazards ratio (95% CI)	P
Performance Status[a]	0.49	0.31	1.63 (0.89–2.99)	0.11
Disease stage	0.36	0.19	1.43 (0.99–2.07)	0.06
Histology (squamous cell)	0.34	0.22	1.40 (0.91–2.16)	0.13
Hemoglobin (g/dl)	−0.09	0.05	0.92 (0.83–1.02)	0.11
Serum LDH (IU/l)	0.001	0.000	1.001 (1.000–1.001)	0.001
Treatment (CTx)	−0.50	0.23	0.61 (0.39–0.96)	0.03
Fighting spirit[b]	0.02	0.02	1.02 (0.99–1.05)	0.16
Total Mood Disturbance[c]	0.002	0.003	1.002 (0.996–1.01)	0.53
Major depression	−0.23	0.46	0.79 (0.32–1.95)	0.61
Number of confidants	−0.01	0.02	0.99 (0.96–1.03)	0.71
Satisfied with confidant	−0.01	0.08	0.99 (0.84–1.16)	0.87

Psychosocial factors were assessed at after diagnosis but before treatment.
CI: confidence interval; LDH: lactate dehydrogenase; CTx: chemotherapy.
[a]As defined by the Eastern Cooperative Oncology Group criteria.
[b]Mental Adjustment Cancer Scale.
[c]Profile of mood states.

Table 3. Multivariate Cox proportional regression analysis

Variable	Coefficient	SE	Hazards ratio (95% CI)	P
Performance Status[a]	0.30	0.31	1.35 (0.74–2.48)	0.33
Disease stage	0.41	0.19	1.50 (1.03–2.19)	0.04
Serum LDH (IU/L)	0.001	0.000	1.001 (1.000–1.001)	0.001
Treatment (CTx)	−0.54	0.24	0.59 (0.37–0.93)	0.03

CI: confidence interval; LDH: lactate dehydrogenase; CTx: chemotherapy.
[a]As defined by the Eastern Cooperative Oncology Group criteria.

A multivariate Cox proportional regression analysis indicated that an advanced clinical stage, a higher serum LDH level, and not receiving chemotherapy were independently associated with a shorter survival period among patients with inoperable NSCLC (Table 3). In addition, we preliminarily conducted a stepwise Cox regression analysis (backward elimination), including the aforementioned five psychosocial factors and six biomedical factors. The findings also indicated that advanced disease stage, a high LDH level, and no chemotherapy were significantly associated with a shorter survival period (data not shown).

Regarding the stability of the psychosocial factors, our findings demonstrated that the correlation coefficients of the fighting spirit subscale of the MAC, the TMD of the POMS, the number of confidants, and the satisfaction with the confidants between T1 and T2 were 0.65 ($P<0.001$), 0.54 ($P<0.001$), 0.45 ($P<0.001$), and 0.18 ($P=0.06$), respectively. These findings suggested a moderate to high stability of most of the psychosocial factors other than the perceived satisfaction with social support.

Discussion

This is the first prospective cohort study to clarify the association between a broad range of psychosocial factors and survival among homogenous patients with advanced NSCLC. The present study has several advantages. First, we assessed most of the well-established biomedical prognostic factors, although the final analysis did not need to adjust for these factors. Second, we first investigated clinical depression using the most reliable method available (a structured clinical interview conducted by a trained psychiatrist). Third, we ascertained the stability of the psychosocial factors subsequent to the cancer diagnosis.

Our results demonstrated that psychosocial factors, including coping with cancer, psychological distress, clinical depression, and social support, are not significantly associated with survival time among inoperable patients with NSCLC. Overall, the findings that a specific coping style, 'fighting spirit', and clinical depression had no significant effect on survival in advanced lung cancer patients should be emphasized because it is commonly believed that a patient's coping with cancer and negative emotions, especially depression, can affect his or her chances of surviving cancer. In addition, because our study confirmed the moderate to high stability of several of the psychosocial factors, we found little convincing evidence that a weak 'fighting spirit' or negative emotions after cancer diagnosis played a clinically relevant role in survival from cancer, even when these findings were stable over relatively long periods of time. Furthermore, our study demonstrates that social support factors do not have an important influence on survival time among advanced lung cancer patients. These findings are consistent with some previous studies and our findings suggest that advanced lung cancer patients need not feel pressured into adopting a specific coping style to cancer or blame themselves for having 'negative emotions and/or depression' after their cancer diagnosis that might affect their survival [37,38]. The present findings may be relevant because the psychological distress experienced by lung cancer patients has been repeatedly reported to be higher than in other cancer patients (see Introduction). Furthermore, this study provides the first findings about clinically diagnosed depression, namely major depression, after a diagnosis of inoperable lung cancer and the subsequent survival time. Although many previous studies have demonstrated a significant association between depression and survival among cancer patients [28,39,40] and patients with other diseases, especially cardiovascular patients [41,42], the current findings are not consistent with the previous findings. This may be partly due to the differences in the subjects and the relatively small sample size (e.g. only six patients suffered from major depression). Further, large studies may be needed to obtain more conclusive findings between clinical depression and survival among lung cancer patients.

Finally, we would like to mention a possible effect of Japanese culture on the findings obtained. In Japan, a diagnosis of cancer is still often considered to be the equivalent of a death sentence, and the disclosure of a cancer diagnosis is not universally practiced [43]. Although the institution at which the present study was conducted is exceptional in that a cancer diagnosis is usually disclosed to the patient, cultural differences in patient–physician communication and the social meaning of a cancer diagnosis may have influenced the psychosocial factors that were investigated and be consequently may be somewhat associated with the present findings. In addition, previous Japanese studies have consistently indicated a somewhat lower prevalence of major depression, ranging between 4 and 7%, among cancer patients,

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compared with findings from Western countries [12,44–46]. Thus, the low prevalence of major depression is unlikely to represent a sampling bias, but rather cultural differences—as discussed in our previous study [12,46].

We would like to emphasize that our findings do not imply that dealing with psychosocial issues among cancer patients in clinical oncology setting is unimportant. As many studies have indicated, psychosocial issues not only cause serious suffering [47], but also worsen the quality of life [48], reduces compliance with anticancer treatment [49], can lead to suicide [50], are a psychological burden on the family [51], and prolongs hospitalization [52].

Although it was not the principal purpose of our study, we would like to note that our findings suggest that the serum LDH level could be a useful independent biomedical prognostic factor of the length of survival among patients with advanced NSCLC. LDH is an enzyme that is released into the peripheral blood after cell death. Therefore, the serum LDH level may represent biomedical conditions associated with the length of survival among patients with advanced NSCLC. A rigorous psycho-oncological study investigating the influence of psychosocial factors on survival may be needed to evaluate these biomedical factors as well as psychosocial factors.

Our study also has some weaknesses. First, since only 53.0% (122/230) of the subjects could be included in the analysis, generalizing the results may be problematic, and the sample size of the follow-up group was not very large. Second, the fact that the patients who participated in the study were more likely to have a better PS than those who did not indicate a potential selection bias. Third, as mentioned above, because the number of cases with clinical depression was quite small, the validity of our findings regarding the association between clinical depression and survival may be limited. To overcome these limitations, we are conducting a large-scale cohort study involving more than 2000 subjects to investigate psychosocial factors and survival among lung cancer patients [53]. Since the present study was conducted at one institution, an institutional bias may be another problem. Because current smoking at the time of lung cancer diagnosis could be an independent predictor of survival and a close association between smoking and emotional distress has been documented [54,55], the lack of data on continuous tobacco use after cancer diagnosis and its relationship with emotional distress and survival may be an additional limitation. Finally, because this study focused on advanced NSCLC cancer patients, the results may not be applicable to patients with other types and/or clinical stages of cancer.

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Etiologies of Delirium and Their Relationship to Reversibility and Motor Subtype in Cancer Patients

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Background: Delirium is one of the most commonly encountered complications in patients with cancer. The etiology of delirium in cancer is often multi-factorial, and few reports have examined the causes of delirium. This study investigated the causes of delirium and their association with reversibility and motor subtypes of delirium in cancer patients.
Methods: The subjects were inpatients with cancer who had been referred to our Department of Psychiatry and diagnosed with delirium by psychiatrists. The causes of delirium were determined using standard operationalized criteria. The association between delirium reversibility and each clinical factor was examined in detail and longitudinally.
Results: Data were available from a total of 100 patients. Among them, 58% had hyperactive delirium and 14% had hypoactive delirium. Delirium improved in 56% of the patients after 1 week of standard treatment. The most frequent causes of delirium were opioids (29%), inflammation (27%), dehydration and/or sodium level abnormalities (15%). While two or more causes were identified in 40% or more of the cases, the cause of delirium was not identified in 20% of the patients. Neither reversibility nor motor subtypes of delirium was associated with any specific etiological factor.
Conclusions: When treating delirium, prevalences of the causes of delirium, as identified in this study, should be kept in mind. Further research is required to investigate what specific treatments may facilitate the prompt recovery from delirium among cancer patients.

Key words: delirium – etiologies – cancer – general ward – reversibility – consultation-liaison

INTRODUCTION

Delirium is an acute and transient disturbance of cortical functioning that manifests as deficits in cognition, attention, consciousness and recent memory. Presenting symptoms and signs usually include insomnia with a disturbance or reversal of the sleep/awake cycle, psychomotor agitation or retardation and sometimes perceptual abnormalities such as illusions or hallucinations.

Delirium is one of the most commonly encountered complications in patients with cancer. It occurs in 25–40% of hospitalized patients and may be seen in up to 80% of patients in the terminal stage of their disease (1–6). Patients with delirium tend to require longer hospital stays and have higher mortality rates (2,7,8). In patients with cancer, delirium imposes an additional burden, as the consequent deficits in awareness and attention impede communication with their families and hinder participation in treatment decisions, counseling and symptom assessment (9–11).

One of the most important strategies for the management of delirium is the early identification of the potential cause of delirium and subsequent treatment. However, the causes of delirium are various, and their clinical identification is difficult. Very few studies have investigated the causes of delirium among cancer patients. In addition, to the best of our knowledge, few studies have examined the relation between the causes of delirium and reversibility. Lawlor et al. (2) investigated the cause of delirium among advanced cancer patients who had been admitted to an acute palliative care unit. They reported that the most common cause of delirium was opioids (76%) and psychoactive medications (21%). Furthermore, opioids and dehydration were associated with delirium reversibility, whereas hypoxic encephalopathy and metabolic factors were associated with the non-reversibility of

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delirium. Morita et al. (4) also investigated the pathologies and clinical features of terminal cancer patients with delirium who had been admitted to hospice care. They identified metabolic failure (e.g. hepatic failure, prerenal azotemia and hyperosomolality: 29%, 21% and 21%, respectively) and medication (25%) as the most common causes of delirium in this population. Furthermore, they suggested that delirium caused by medication and hypercalcemia is more likely to improve significantly with treatment. In addition, Gaudreau et al. (12,13) reported in a prospective cohort study that opioid exposure significantly increased the risk of delirium (odds ratio of 1.7) in hospitalized cancer patients.

In clinical oncology settings, the management of patients with delirium is often done through psychiatric consultation at the general wards. However, no studies have investigated the causes of delirium in psychiatric consultation settings. Because these previous studies described above were conducted in palliative care settings, the generalizability of their findings may be limited. For example, the active treatment is scarcely done there. In addition, the method used to identify the etiology of delirium was not clear, and operational diagnostic criteria such as the DSM were not applied in one study (14).

The clinical manifestations of delirium vary widely but may be classified as hyperactive, hypoactive or mixed subtypes, depending on the symptomatology, especially the level of psychomotor activity and alertness. Hyperactive patients are agitated, restless and very distracted, and they respond to stimuli with discrimination. These patients may even be physically combative. Hypoactive patients are quiet, inactive and lethargic, with an overall reduction in their responses to stimuli (15–18). Several studies have suggested that hyperactive, hypoactive and mixed delirium subgroups may differ according to etiology, pathophysiology, detection rates, delirium treatment experience and duration of episodes and outcome (19–22). As far as we know, few studies have addressed the association between the cause of delirium and the clinical subtype in cancer patients.

The purposes of this study were to determine the precipitating etiologic factors of delirium and the reversibility of delirium originating from each different cause in a psychiatric consultation setting. We also investigated the association between each precipitating factor and the clinical subtypes.

PATIENTS AND METHODS

Study Population

This study was conducted at Nagoya City University Hospital, an 808-bed teaching and tertiary care facility of the Nagoya City University Medical School in Aichi, Japan. The subjects included in this study were consecutive adult cancer patients who were referred to the Department of Psychiatry in a consultation-liaison setting between August 2005 and December 2007. All the patients had been hospitalized in general medical wards other than the psychiatric or pediatric wards.

The eligibility criteria were an age of 18 years or over, a confirmed diagnosis of cancer and fulfillment of the criteria for delirium according to the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) (23) as determined by a trained psychiatrist. The exclusion criteria were a post-operative period of within a fortnight, recent withdrawal from a respirator, underlying obvious dementia and the presence of intracranial disease such as brain metastasis or a cerebral vascular accident. Because this study aimed to examine the relationship between the cause of delirium and the responsiveness to treatment, cases whose delirium was thought to be associated with the above-mentioned exclusion criteria were excluded.

Since this research was performed using data collected during routine clinical practice, informed consent and Institutional Review Board approval were not obtained.

Procedure

First, we evaluated the global condition of patients, the severity and motor subtypes of delirium and its precipitating factors at baseline (when the delirium was first diagnosed). At the same time, we also asked patients' physicians, nurses or caregivers about the overall physical functioning of the patients to evaluate patients' performance status. A structured evaluation was performed, and we evaluated the time–dosage relation between delirium and factors at the time of delirium deterioration. These evaluations were performed by two trained psychiatrists (R.S. and T.O.) Then, standard therapy for delirium (24) was performed. Two main approaches were utilized: symptomatic therapy using antipsychotics such as haloperidol or risperidone (25–31), and reporting the potential cause of delirium to the attending physician and requesting medical treatment, if possible. A follow-up investigation was conducted 1 week later, at which time the severity of the delirium and delirium-related factors were evaluated.

Precipitating Factors and Criteria for Cause Identification

To investigate the biological precipitating factors for the development of delirium, we utilized an *a priori* list of precipitating factors developed using literature references and examined all the listed items using a data entry sheet that we developed.

Each potential precipitating factor for delirium was assessed with regard to the following three criteria (2,7,32). Criterion 1 was the evidence of its presence based on specific clinical and laboratory data. Criterion 2 was a temporal association with the course of delirium consistent with a precipitating factor. Criterion 3 was the improvement of delirium or its non-improvement corresponding to evidence of amelioration or continuation, respectively, of the precipitating factor. When the factor met all three criteria, it was judged to be the most probable precipitating factor of