

## Original Article

# Prevalence, course and factors associated with delirium in elderly patients with advanced cancer: a longitudinal observational study

Megumi Uchida<sup>1,2</sup>, Toru Okuyama<sup>1,2,\*</sup>, Yoshinori Ito<sup>1,2</sup>,  
Tomohiro Nakaguchi<sup>1,2</sup>, Mikinori Miyazaki<sup>3</sup>, Masaki Sakamoto<sup>2,4</sup>,  
Takeshi Kamiya<sup>5</sup>, Shigeki Sato<sup>3</sup>, Hiromitsu Takeyama<sup>4</sup>, Takashi Joh<sup>5</sup>,  
David Meagher<sup>6</sup>, and Tatsuo Akechi<sup>1,2</sup>

<sup>1</sup>Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, <sup>2</sup>Division of Palliative Care and Psycho-oncology, Nagoya City University Hospital, Nagoya, <sup>3</sup>Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Sciences, Nagoya, <sup>4</sup>Department of Gastroenterological Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, <sup>5</sup>Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, and <sup>6</sup>Graduate Entry Medical School, University of Limerick, Limerick, Ireland

\*For reprints and all correspondence: Toru Okuyama, Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya, Aichi 467-8601, Japan. E-mail: okuyama@med.nagoya-cu.ac.jp

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## Abstract

**Objective:** The aim of this study was to investigate the prevalence of delirium on admission, the course of delirium during a 2-week period after admission and factors associated with delirium on admission, among elderly patients with advanced cancer.

**Methods:** Patients aged  $\geq 65$  years with incurable lung or gastroenterological cancer and the Eastern Cooperative Oncology Group Performance Status 2 or greater were continuously sampled after admission to a university hospital. Participants were evaluated for DSM-IV-TR delirium by trained psychiatrists and the delirium subtype was assessed using the Delirium Motor Subtype Scale within 4 days after admission and again 2 weeks later. In addition, we assessed associated factors with delirium on admission.

**Results:** Among 73 eligible patients, complete data were available from 61 on admission and 49 after 2 weeks. Twenty-six patients (43%) met delirium criteria on admission (hypoactive: 58%, unspecified: 35%, hyperactive: 4%, mixed: 4%). Of these, 19 (73%) remained delirious 2 weeks later. Of 35 patients without delirium on admission, 21 (60%) remained delirium-free 2 weeks later and 7(20%) became delirious. Overall, 33/61 (54%) developed delirium at some point during the study. Patients receiving steroids at admission were more likely to have delirium (odds ratio = 5.0; 95% confidence interval = 1.5–16).

**Conclusions:** Given the high prevalence of the delirium, all patients with advanced cancer should be screened for delirium both on admission and regularly thereafter. In addition, medical staff should be aware that steroid use on admission is an additional indicator of elevated risk for delirium.

**Key words:** delirium, advanced cancer, prevalence, associated factor, course

## Introduction

Delirium is a complex neuropsychiatric syndrome that is highly prevalent among elderly hospitalized patients (1,2) and that adversely impacts on mortality, functional decline, incidence of falling, institutional admission, increased length of hospital stay and medical cost (1,3–6). In addition, delirium is a significant cause of distress to patients and family members, caregivers and medical/nursing staff (7,8).

In elderly patients with advanced cancer, delirium impairs recognition of physical symptoms, and complicates efforts to achieve optimal symptom management, especially pain control (9). Moreover, delirium inhibits communication and has an effect on decision-making (10). Thus, the importance of interventions to prevent and treat delirium among patients with advanced cancer has been increasingly recognized. And understanding the prevalence and course of the disorder is imperative to develop intervention strategies for delirium.

Previous studies conducted at palliative care wards/hospice facilities clarified that the prevalence of delirium was 28–47% (11–15). As for delirium in general medical wards, they reported that the prevalence was 18–35% and the incidence was 3–29% (1,3). Few studies, however, reported prevalence and courses of delirium among advanced cancer patients at non-palliative care or hospice setting.

The objective of this study was to investigate the prevalence of delirium on admission, the course of delirium during a 2-week period after admission and associated factors useful to identify delirium among elderly patients with advanced cancer on admission in general medical wards. The National Institute for Health and Clinical Excellence recommends screening of all patients at high risk which includes those with any of four risk factors; namely, age  $\geq 65$  years, dementia, presentation with hip fracture and severity of illness (16). Therefore, we targeted inpatients aged  $\geq 65$  years with incurable advanced cancer and The Eastern Cooperative Oncology Group Performance Status (ECOG PS) of  $\geq 2$ .

## Patients and methods

### Subjects

The patients were sampled consecutively within 4 days after admission. The study subjects were inpatients with lung or gastroenterological cancer admitted to the general medical ward of Nagoya City University Hospital (Nagoya, Japan) between October 2008 and March 2011. The eligibility criteria for inclusion in this study were: (i) incurable lung or gastroenterological cancer; (ii) age  $\geq 65$  years; (iii) planned hospital admission of  $\geq 2$  weeks; and (iv) ECOG Performance Status of 2 or worse (i.e. ranging from ambulatory and  $< 50\%$  of daytime in bed with impaired daily activities to being unable to perform self-care, and totally confined to a bed or chair). We targeted these patients because of their vulnerability to delirium. The exclusion criteria were follows: (i) physically too ill to complete the survey and (ii) inability to understand the Japanese language. Though we included as many patients as possible, we could not help but exclude the subjects who were not able to complete the survey at all from an ethical perspective.

The study protocol was approved by the Institutional Review Board and Ethics Committee of Nagoya City University, Graduate School of Medical Sciences, and was conducted in accordance with the principles of the Declaration of Helsinki. Written consent was obtained from each patient after receiving explanation on the study. For patients with impaired competence, we obtained both oral consent from the patient and written consent from appropriate proxies.

### Procedure

After obtaining informed consent, we evaluated for delirium, including the diagnosis, illness severity and motor subtype at baseline within 4 days of admission. At this time, we gathered information on the overall physical/psychological function of each patient from physicians, nurses and caregivers. In addition, we referenced medical records to assess factors associated with delirium. These evaluations were performed by two trained psychiatrists (M.U. and T.O.) and one trained psychologist (Y.I.). A follow-up assessment was conducted 14 days later. During the period, participants could receive usual care and treatment for delirium including pharmacotherapy and referral to psychiatrists and/or palliative care team.

### Study measures

Delirium diagnosis was conducted by two trained psychiatrists (M.U. and T.O.) according to DSM-IV-TR criteria and based upon a full neuropsychiatric assessment. Before we started the study, we made diagnosis of a few patients and adjusted them between psychiatrists to enhance the reliability.

### Delirium Motor Subtype Scale

The attribution of motor subtype was made using the Delirium Motor Subtype Scale (DMSS) (17). This is a 13-item, clinician-rated scale that allows for subtype attribution that has demonstrated concurrent and predictive validity (18). It was originally developed in palliative care patients but has also been validated in CL-Psychiatry and elderly medical and surgical patients. (19) A Japanese version was translated by two trained psychiatrists.

Clinical information used to determine the subtype was collected with regard to the mental status of the patient in the previous 24 h period. Patients were classified as 'hyperactive' subtype if they exhibited two or more of the following five criteria: increased activity levels, increased speed of actions, loss of control of activity, restlessness and wandering. Patients were classified as 'hypoactive' subtype if they exhibited two or more of the following eight criteria: decreased activity, decreased speed of actions, apathy/listlessness, decreased speech, decreased speed of speech, decreased volume of speech, decreased alertness and withdrawal/unawareness. Patients were categorized as 'mixed' subtype if they met the criteria for both the hyperactive and hypoactive subtypes. Patients were categorized as 'no subtype (unspecified)' if there was no indication of either the hyperactive or hypoactive subtype.

### The Revised Delirium Rating Scale

The Revised Delirium Rating Scale (DRS-R-98) is a 16-item, clinician-rated scale to measure symptom profile in delirium that can be used for both diagnostic and severity assessment (20). The severity scale has 13 items, each rated from 0 to 3 points with a maximum of 39 points, where higher scores reflect greater severity of delirium. Three diagnostic items (rated from 0 to either 2 or 3 points) capture the temporal course and attribution to an underlying etiology and when added to the sum of the 13 symptom items produce a DRS-R-98 total score ranging from 0 to 46 points. The original validation study suggested cut-off scores for a differential diagnosis of 18 points on the total scale and  $\sim 15$  points for the severity scale. However, milder forms of delirium can occur with scores  $\geq 11$  points. Validity and reliability were confirmed using the Japanese version of the DRS-R-98 (21).

## Factors associated with delirium on admission

To assess factors that might assist in the identification of patients at higher risk of delirium on admission, we documented a number of potential associated factors based upon the literature (11,22–25) and confirmed each from patient medical records and interviews. Because we assumed that these factors would be easy to monitor in clinical oncology settings, we selected items detailed in a previous study (26).

## Predisposing factors for delirium

Cerebrovascular disease and dementia were considered as general predisposing factors in this study.

## Organic precipitating factors

**Primary cerebral disease:** Brain metastasis was included as a precipitating factor in this study.

**Exposure to psychoactive medications:** Medical records were reviewed for use of opioids, benzodiazepines and steroids.

**Blood test:** We utilized blood test results if those measured within seven days before or after the first assessment were available. The data included blood levels of creatinine, urea nitrogen, sodium, aspartate aminotransferase, alanine aminotransferase I, bilirubin, glucose, calcium (corrected for the albumin level), lactate dehydrogenase, white blood cells, C-reactive protein hemoglobin and platelet count.

## The Eastern Cooperative Oncology Group Performance Status

Patients' daily living ability performance status was assessed with the Eastern Cooperative Oncology Group Performance status (ECOG PS). The ECOG PS scale is an one-item scale, and it ranges from 0 to 4, with higher scores indicating more difficulty with activities of daily living. Although constructed for use in oncology patients, it has been applied to broader medically ill patient populations to assess the severity of their physical condition.

## Sociodemographic and medical factors

Sociodemographic data, including marital status, education level and employment status, were collected. ECOG PS and expected survival time (<6 vs. ≥6 months) were evaluated by the attending physicians. Clinical stage was obtained from medical records.

## Statistical analysis

The subjects were classified into two groups according to the presence of DSM-IV-TR delirium on admission. To identify potential factors associated with delirium, all investigated variables were divided into two groups (e.g. education, <12 vs. ≥12 years; creatinine >1.3 vs. ≤1.3 mg/dl) as written in the previous study (26) because this simple dichotomization can assist the medical staff to easily evaluate patient characteristics and symptoms in daily routine practice. One exception was for blood sugar level which was divided into three categories.

All investigated variables were included in the preliminary univariate analysis to identify associations between delirium and investigated factors using  $\chi^2$  test and/or Fisher's exact test, as appropriate. To identify the final associated factors with delirium, variables with a probability (*P*) value <0.10 in the univariate analysis were entered into a logistic regression model as independent variables. A two-tailed *P* value <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS statistical software (version 22; IBM SPSS, Inc., Chicago, IL, USA).

## Results

### Patient characteristics

Of the 73 eligible patients, complete data were available for 61 (83%) on admission and 49 (67%) at 2 weeks after admission. Twelve patients (directly or through a family member) refused to participate in the study. (3: poor physical condition, 4: no reasons expressed, 5: others) We did not find significant differences in respect of disease-related (cancer site, PS, clinical stage) and sociodemographic (age, sex) factors between those who participated in the study and those who did not.

Characteristics of the 61 patients included in the study are listed in Table 1. Non-small-cell lung cancer (*n* = 34, 47%) and small-cell lung cancer (*n* = 10, 14%) were the most common cancers and 75% of the patients received a terminal prognosis indicating a likely survival time of <6 months.

### Prevalence of delirium

Among the 61 included patients, 26 (43%) met DSM-IV-TR criteria for delirium on admission (Table 1). According to the DMSS, 15 patients (58%) exhibited hypoactive delirium, one (4%) had hyperactive delirium, one (4%) was classified with the mixed subtype and nine (35%) were classified with an unspecified subtype (Fig. 2). The

**Table 1.** Characteristics of the study participants on admission (*n* = 61)

Characteristic	<i>n</i>	(%)
Age		
Mean: 72 years (SD = 6)		
Median: 72 years (range, 43–85 years)		
Sex		
Male	45	74
Marital status		
Married	52	85
Education		
≥12 years	37	61
Employment status		
Full time	12	20
Original cancer site		
Lung	45	74
Gastroenterological	15	25
Clinical stage		
Locally advanced	9	15
Metastatic	48	79
Recurrence	1	2
Unknown	3	5
ECOG PS <sup>a</sup>		
2	25	41
3	24	39
4	12	20
Estimated prognosis assessed by attending physicians		
<6 months	46	75
Delirium defined by DSM-IV-TR	26	43
Delirium motor subtype <sup>b</sup>		
Hypoactive	15	58
Hyperactive	1	4
Mixed	1	4
Unspecified	9	35

<sup>a</sup>Defined by Eastern Co-operative Organization Group Performance Status (ECOG PS).

<sup>b</sup>Defined by Delirium Motor Subtype Scale (DMSS) (17).

2 Weeks later			Delirium				Without delirium	No second assessment
			Hyperactive	Hypoactive	Mixed	Unspecified		
			2	21	1	2		
On admission								
Delirium	Hyperactive	1	0	1	0	0	0	0
	Hypoactive	15	0	9	1	0	1	4
	Mixed	1	0	1	0	0	0	0
	Unspecified	9	1	5	0	1	1	1
Without delirium		35	0	1	6	0	21	7

Figure 1. The course of delirium subtype.

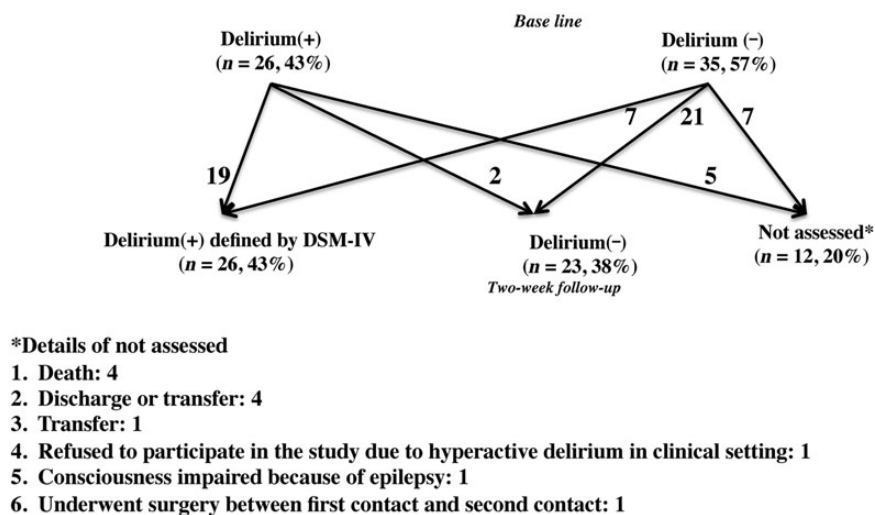


Figure 2. The prevalence and course of delirium.

mean DRS-R98 total score was  $16.5 \pm 5.6$  and the mean DRS-R-98 severity score was  $11.8 \pm 5.6$  among patients with delirium. DRS-R98 score of unspecified type was significantly lower than those of the other motor subtypes (unspecified:  $12.67 \pm 5.074$ , others:  $18.59 \pm 4.836$ ,  $t = -2.922$ ,  $P = 0.007$ ).

### Course of delirium

Among the 26 patients with delirium on admission, at 2-week follow-up, 19 (73%) remained delirious, four (15%) had died, delirium resolved in two (8%) and one (4%) was discharged from the hospital after 2 weeks (Fig. 1). Of the 35 patients without delirium on admission, 21 (60%) remained delirium-free, seven (20%) exhibited delirium, five (14%) were discharged from the hospital, one (3%) was transferred to another hospital and one (3%) died 2 weeks after admission (Fig. 2). Among patients with delirium, six patients (23%) took antipsychotics on admission and 12 patients (46%) did 2 weeks later.

Subtypes were consistent at 2-week follow-up in 53% (10/19) of patients (47% hypoactive, 5% unspecified subtype) and 47% (9/19) had a variable subtype course. Fifteen patients received antipsychotics

for delirium and 12 patients underwent psychiatric consultation during the 2-week period.

### Delirium-associated factors on admission

Univariate analysis indicated that steroid use and male sex were significantly associated with the presence of delirium among inpatients with advanced cancer, whereas other demographic characteristics and biomedical factors were not (Table 2). These patterns were also evident with multivariate analysis (Table 3).

## Discussion

### Overall summary

To our knowledge, this study is the first to investigate the prevalence, course and factors associated with delirium in elderly general hospital in-patients with advanced cancer on admission not under specialist palliative/psychiatric care. In this longitudinal observational study, the prevalence of delirium was high, including on admission (43%) among this highly vulnerable population. Over 2-week follow-up,

**Table 2.** Factors associated with delirium on admission by univariate analysis (*n* = 61)

	Delirium				<i>P</i>
	Present ( <i>n</i> = 26)		Absent ( <i>n</i> = 35)		
Age	Mean: 72 years (SD = 4.7) <i>N</i> %		Mean: 72 years (SD = 7.5) <i>N</i> %		0.87
Sex (male)	23	88	22	63	0.03
Cancer site (lung)	20	77	25	71	0.76
ECOG PS					
2	10	38	15	43	0.92
3	11	42	13	37	
4	5	19	7	20	
Education (≥12 year)	15	58	22	63	0.71
Delirium predisposing factors					
Dementia	1	4	1	3	0.68
Cerebrovascular disease	1	4	3	9	0.43
Delirium precipitating factors					
Brain metastasis	10	38	9	26	0.29
Medication					
Opioid	10	38	12	34	0.80
Benzodiazepine	6	23	9	26	0.76
Steroids	15	58	7	20	0.03
Dehydration					
Creatinine >1.3	2	8	4	11	0.47
BUN >20	7	27	12	34	0.49
Na <135	6	23	5	14	0.31
Metabolic factor					
Blood sugar <72	4	15	1	3	0.19
73–180	19	73	26	74	
>180	2	8	5	14	
AST >40	7	27	5	14	0.24
ALT >50	3	12	1	3	0.21
Bilirubin >1.1	6	23	3	9	0.12
Creatinine >1.7	1	4	2	6	1.00
Calcium >10.4	3	12 <sup>a</sup>	4	14 <sup>a</sup>	0.59
LDH >430	5	19	4	11	0.33
Inflammation					
WBC >8500	6	23	10	29	0.58
CRP >0.3	23	88	28	80	0.46
Anemia					
Hemoglobin <10	8	31	14	40	0.36
Clotting abnormality					
Platelets <150 000	2	8	7	20	0.14

BUN, blood urea nitrogen Na: sodium; AST, aspartate aminotransferase ALT, alanine aminotransferase; LDH, lactate dehydrogenase; WBC, white blood cell; CRP, C-reactive protein.

<sup>a</sup>Percentages are computed based on the total number of non-missing cases.

Bold value shows a significant association (*P* < 0.05).

**Table 3.** Associated factors with delirium on admission logistic regression analysis (*n* = 61)

	$\beta$	SE	Odds ratio	95% CI	<i>P</i>
Male gender	1.5	0.75	4.4	1.0–19.2	0.048
Steroids	1.6	0.61	5.0	1.5–16.4	0.008

CI, confidence Interval.

the vast majority (88%) of patients with delirium upon admission experienced either persistent delirium (73%) or died (15%). Steroid use and male sex were significantly associated with delirium on admission. Twenty percent of those who were delirium-free at admission subsequently developed delirium over 2-week follow-up.

### Prevalence of delirium

Although our participants were sampled from general medical wards, the prevalence of delirium in our study was similar to that reported in previous studies of patients with advanced cancer in palliative care units (11,12). This emphasizes the need to screen all elderly hospitalized patients for delirium, with particular attention warranted to those with cancer diagnoses, including careful screening at admission.

Delirium in this population was predominantly hypoactive in profile. This echoes previous studies that indicate relative hypoactivity in patients developing delirium in palliative care settings compared with consultation-liaison psychiatry or elderly medical patients (12,27). The proportion of cases of delirium that were hypoactive in profile increased over the 2-week follow-up from 58 to 81%. This principally reflected the transition from unspecified subtype to hypoactive subtype. Previous study has suggested that the unspecified or 'no' subtype is frequently milder in severity as it reflects evolving or resolving delirium (14) and our findings indicated that patients with 'no' subtype had lower delirium severity ratings that were borderline between subsyndromal and mild delirium. The preponderance of hypoactive delirium in this population poses an additional challenge in terms of accurate diagnosis, as it can be difficult to distinguish from depression and dementia, with studies indicating considerable diagnostic overlap (28,29). In addition, hypoactive delirium is much less compelling in presentation and can be easily overlooked in busy ward settings where the 'good' or compliant patient is often presumed to be cognitively intact (30). Therefore, it is important to develop clear assessment procedures for timely detection of delirium and to provide training to nurses to recognize hypoactive delirium (31).

### Course of delirium

In the present study, ~40% of the patients exhibited delirium on admission and ~75% of these remained delirious over a 2-week follow-up period. Although delirium is typically considered to be a condition with substantial reversibility—even in palliative care patients where previous work indicates 30–50% of cases are reversible (11,32)—we found low reversibility over a 2-week follow-up period in this highly morbid general hospital population. This may relate to the high morbidity in this population as well as the preponderance of hypoactive delirium which typically has a worse prognosis and is generally thought to be less responsive to antipsychotic medications (27). Increasingly, the need for earlier detection and treatment of delirium is advocated with a recent study indicating that mortality in elderly medical patients is increased by 11% for each additional 48 h of active delirium (33).

### Delirium-associated factors on admission

We found an increased prevalence of delirium on admission among patients with cancer who used steroids or were of male gender. Few studies have identified factors that are useful to detect delirium in patients with cancer on admission. Sarhill et al. (34) reported that brain metastases and the use of anticancer drugs were the most common predisposing factors of delirium among patients with advanced cancer on admission. However, this report did not include statistical analysis to investigate potential confounding effects/correlations. In contrast, our study identified steroid as useful indicators for medical staff in the care

of in-patients with cancer using the appropriate statistical methods, although the previous research found inconsistent results regarding association between steroids and delirium among cancer patients (22,23,35). Mean dosage of corticosteroid in prednisolone equivalent is  $46.0 \pm 72.8$  mg/day. As the sample size is too small, we could not investigate the association between its dosage and delirium. Health-care staffs frequently experience difficulty to detect delirium (30,36). Furthermore, many patients under palliative care receive steroid therapy. Given the high prevalence of delirium in this setting, medical staff should routinely screen all patients, with special attention to the patients receiving steroids on admission.

### Study limitations

There were several limitations associated with this study. First, the sample size was small. Second, we studied patients at a tertiary hospital and as such, the results may not generalize to other settings. Third, we assessed patients only twice over a period of 2 weeks (on admission and ~2 weeks later) which may underestimate symptom burden as delirium is typically highly fluctuating in nature. Fourth, validity of Japanese version of the DMSS was not confirmed. Fifth, we did not include the data of anticholinergic, antiemetic, sedative and chemotherapy drug. Finally, bias may have occurred because the investigator was not blinded to the patients' characteristics.

### Study strengths

Despite these limitations, this study had several strengths. For example, the response rate was relatively high (83%) and we used reliable and validated assessment tools. In addition, psychiatrists confirmed the diagnosis of delirium after a detailed assessment. Finally, because we sampled patients in general medical wards including usual delirium treatment by both attending physicians and consultation with psychiatrists, our findings are typical of real-world practice and readily generalizable to medical wards in general hospitals.

### Conclusions

In conclusion, in this longitudinal observational study, the prevalence of delirium among elderly patients with advanced cancer was high on admission and persisted for the majority at 2-week follow-up. These findings emphasize the need for careful and systematic screening for delirium including predisposing factors in elderly patients with advanced cancer both at admission and throughout the period of hospitalization. We also found that steroid use on admission was significantly associated with delirium, emphasizing its possible role as an indicator of elevated delirium risk.

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### Conflict of interest statement

None declared.

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## Appendix

In addition to the authors listed on the first page, the following author contributed equally to this study.

Nobuhiro Sakamoto: Division of Palliative Care and Psycho-oncology, Nagoya City University Hospital, Nagoya, Japan; Department of Gastroenterological Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.