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Patients' perception of the usefulness of a question prompt sheet for advanced cancer patients when deciding the initial treatment: a randomized, controlled trial

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Abstract

Objective: The objective of this study was to evaluate the patients' perception of the usefulness of a question prompt sheet (QPS) in facilitating the involvement of advanced cancer patients during consultation.

Methods: Advanced cancer patients attending their first consultation after diagnosis were randomly assigned to the intervention group (received QPS and a hospital introduction sheet (HIS)) or the control group (received HIS only). Analysis was conducted on an intention-to-treat basis. The primary outcome measure was patient rating of the usefulness of the material(s) (numerical rating scale of 0–10).

Results: Sixty-three advanced cancer patients (72.4% response rate) were enrolled and analyzed. Nearly three-quarters of patients in both groups read the material(s) before consultation. The rated usefulness of the material(s) for asking questions of physicians was significantly higher in the intervention group than in controls (4.4 ± 3.6 and 2.7 ± 2.8 , respectively; $p = 0.033$). The mean score of the usefulness of the material(s) for understanding the treatment plan tended to be higher in the intervention group than in the controls (4.9 ± 3.6 and 3.3 ± 2.8 ; $p = 0.051$). The mean score of willingness to use the material(s) in the future was significantly higher in the intervention group than in the controls (5.3 ± 3.8 and 2.8 ± 2.8 ; $p = 0.006$). There were no significant differences between the groups in the average total number of questions asked by patients (median, 1.0; interquartile range in both groups, 2.0).

Conclusions: QPS provided before oncology consultation may be useful for advanced cancer patients, on the other hand, it did not directly promote patient confidence to ask questions.

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Introduction

In cancer care, good communication is essential for building patient–physician relationship. Patient-centered approaches have been proposed for improving communication between patients and physicians, including the use of a question prompt sheet (QPS) [1–5].

A QPS is a structured list of questions covering the items a patient may want to ask their physicians regarding their illness and treatment. Patients are given the QPS before consultation for them to read and to determine which questions they would like to ask. In cancer setting, randomized controlled

trials have been performed to evaluate the effectiveness of QPS in encouraging cancer patients regardless of the cancer stage to obtain more information about their illness and its treatment. Patients who received QPS asked more questions [6,7] and rated the QPS as significantly more useful for the family [6] as well as more helpful in aiding communication with their physician compared with a control group [8]. However, the patients in the previous randomized studies were commonly at an early disease stage as opposed to the metastatic stage, and their prognosis was typically in the order of years (i.e., 1–5 years), except in one study examining palliative care patients [7,9].

Decision making in patients at the time of initial diagnosis of advanced cancer is quite different than for patients with early stage cancer who are receiving treatments with curative intent or for those with advanced cancer who are already approaching the terminal phase of their illness [10]. Patients who have just been diagnosed with advanced cancer are stunned by the news of having incurable cancer and by the prospect of limited life expectancy [11]. Nevertheless, they are often obliged to make urgent decisions, and this may require an exhaustive search for information about their condition. When deciding on the initial treatment, good communication between an advanced cancer patient and a physician is very important to achieve a better understanding of the medical condition and for the patient to take a more autonomous role in medical care. Therefore, it is important to investigate whether QPS can help advanced cancer patients to ask questions and to collect information when making decisions.

Moreover, Dimoska *et al.* point out that the lack of research examining the use of a QPS by non-English-speaking cancer patients. There are no cancer-specific QPSs that have been translated to other languages [9]. Our previous studies in Japan found that some patients preferred that physicians give them a chance to ask questions, while others did not know what questions to ask and wanted to know the questions most frequently asked by other patients [12,13]. In Japan, it might prove helpful to provide cancer patients with a QPS containing sample questions commonly asked.

In previous QPS studies, the number or duration of questions asked by patients showed a poor correlation with subjective outcomes such as satisfaction [14,15]. Bruera *et al.* described that patient expectations were frequently not met and patients are often not satisfied with information needs [8]. Better communication may not depend on number or duration of questions patients ask. Therefore, in the current study, we investigated the patients' perception of the usefulness of a QPS provided to patients newly diagnosed with advanced cancer in helping them to decide on their initial treatment. Our primary goal was to specifically determine how useful patients found the QPS compared with a hospital introduction sheet (HIS) containing a space in which patients could write their questions freely.

Patients and methods

Setting and participants

The study was performed in the National Cancer Center Hospital East, Japan from February to December 2008. The enrolled subjects were patients with advanced cancer (i.e., locally advanced,

metastatic, recurrent) presenting for their first consultation with an oncologist at thoracic oncology division or gastrointestinal oncology division to discuss the treatment plan. We consecutively recruited patients with advanced nature of the cancer identified from the referral note from their previous physician. Some patients were excluded after recruitment because they were diagnosed as cancer in early stage. The inclusion criteria for the potential patients were as follows: (1) informed of advanced cancer diagnosis, (2) aged 20 years or older, (3) no serious physical or psychological distress recognized by the primary physicians or researchers, (4) no cognitive disorder, (5) able to communicate in Japanese.

Procedure

The potential patients were invited to participate consecutively by their initial physician during the consultation. Thereafter, patients were informed of the purpose and requirements of the study by a researcher. After obtaining written consent, patients were randomly given an envelope, which assigned them to either the intervention group (received QPS and HIS) or the control group (received HIS only). Patients in both the groups were instructed to read the material(s) before their next consultation. Following the next consultation, patients in both groups were asked to complete a questionnaire that assessed the usefulness of the material(s) and their level of satisfaction with the consultation. In addition, the patients were asked about the number and content of the questions for their physician (Figure 1).

The study was approved by the ethics committees of the National Cancer Center, Japan, and registered with UMIN-CTR, number 000001047 (<https://center.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000001254&type=summary&language=E>).

Question prompt sheet

We prepared an initial draft of QPS that contained 63 questions based on previous QPS studies [3,8,14,15] and our previous study on the preferences of Japanese cancer patients regarding the disclosure of bad news [12]. Before the study, we performed interviews with 14 cancer patients and five oncologists and made modifications to the QPS, which included removal of 15 similar questions, addition of five extra questions and some minor changes. The final QPS was a 10-page A4 sheet containing 53 questions grouped into 10 topics and a space for new questions (see Appendix A for the questions of the final QPS).

Hospital introduction sheet

The HIS was designed to provide information on the various services and the faculty of the National

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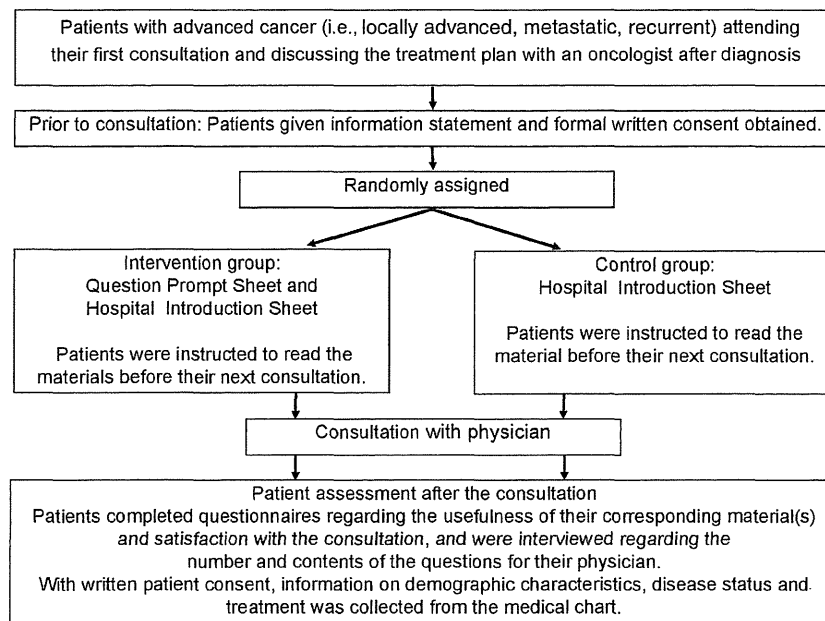


Figure 1. Study procedure

Cancer Center Hospital East, Japan. In addition, the HIS provided information on treatment and contained a space for any questions or messages the patients may have wanted to write.

Measures

Usefulness of the material(s)

Based on a previous study [8], we asked three questions regarding the usefulness of the material(s). Patients were asked to rate the following (assessed by a numerical rating scale of 0 to 10 where 10 represents completely agree and 0 represents completely disagree): (1) the material helped me to ask relevant questions of physicians; (2) the material was useful in understanding the treatment plan; and (3) I will use the material before any consultation in the future.

Satisfaction with the consultation

Patient satisfaction with the consultation was assessed using five items adapted from a previous study [8]. Patients were asked to rate the following (assessed by a numerical rating scale of 0 to 10): (1) the physician answered all the questions; (2) I was able to ask all the questions I wanted to ask; (3) I was able to understand the condition of my disease; (4) I was able to comprehend the treatment plan; and (5) I am satisfied with the consultation.

Number and contents of the questions

The number and contents of the questions were measured by interview immediately after the consultation. We did not use audiotape to record the consultation as in previous studies because audiotaping of consultations is an extremely rare practice in Japan. We feared that audiotaping may

not be acceptable to patients and physicians and may adversely affect recruitment to the study. We asked the patients the following questions and determined the estimated number of patient questions: Did you ask the physician some questions? If so, what kind of questions did you ask? For example, if patient answered that he asked the physician about the side effect and the cost of treatment, we estimated the number of patient questions at 2.

Patient characteristics

With written patient consent, information on demographic characteristics, disease status and treatment was collected from the medical chart.

Sample size calculations

The primary outcome measure was the patient rating of the usefulness of the material(s). Based on a previous study [8], we calculated sample size using the following parameters: 80% power, 0.05 level of significance, 5.70 average score of usefulness increasing to 7.90, with 3.08 as standard deviation. The sample required to detect this difference was 32 per arm. Therefore, the required total sample size was 64 patients.

Statistical analysis

Statistical analysis was conducted on an intention-to-treat basis. The primary outcome measure was patient rating of the usefulness of the material(s). The secondary outcome measures included satisfaction with the consultation, number of total questions and frequency of questions. Differences

in each outcome measure between the intervention group and the control group were measured using independent sample *t*-tests. Proportions in the two groups were compared using Fisher's exact test or Chi-square test. Statistical analysis was conducted using SPSS for Windows version 15 (SPSS Inc., Chicago, IL, USA), with two-tailed statistical tests.

Results

Participant flow, assignment and follow-up

Eighty-seven eligible patients were identified and invited to participate in the study, and 63 consented (72.4%, Figure 2). Non-consent of patients was primarily due to their being too stressed mentally or being severely ill physically. Of the 63 patients [intervention group ($n = 32$); control ($n = 31$)], two (one in each group) had no consultation, one (control group) changed hospitals, and one (intervention

group) withdrew because of mental stress. Thus, a total of 59 patients were analyzed. Strict intention-to-treat analysis was conducted on all randomly assigned 63 patients using all available data from the patients. Dropout, partial absence of data, and failure to use the sheets were included in the analysis as score or number '0'. Patient demographics and clinical characteristics are shown in Table 1. Differences in these variables between groups were not significant.

Approximately 75% of the patients in both groups read their respective material(s) prior to consultation. Forty-four percent of the patients in the intervention group and 23% of the patients in the control group decided on their questions in advance ($p = 0.075$).

Usefulness of the material(s)

The mean usefulness rate (a numerical rating scale of 0 to 10) of the material(s) in helping the patients to ask questions was significantly higher in the intervention group than in the control group (4.4 ± 3.6 and 2.7 ± 2.8 , respectively; $p = 0.033$). The mean score of usefulness of the material(s) in helping the patients to understand the treatment plan tended to be higher in the intervention group than in the control group (4.9 ± 3.6 and 3.3 ± 2.8 , respectively; $p = 0.051$). The mean score of willingness to use the material(s) in the future was significantly higher in the intervention group than in the control group (5.3 ± 3.8 and 2.8 ± 2.8 , respectively; $p = 0.006$; Table 2).

For reference, we conducted treatment analysis including only patients who had read the material(s)

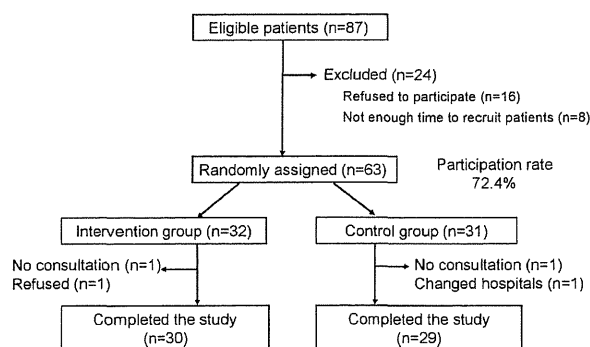


Figure 2. CONSORT diagram

Table 1. Demographics and clinical characteristics of patients ($n = 63$)

		Intervention ($n = 32$), n (%)	Control ($n = 31$), n (%)	Test result
Age, years	Median (range)	63.5 (52–82)	64.0 (28–82)	n.s.
Sex	Male	21 (65.6)	21 (67.7)	n.s.
Type of cancer	Lung	20 (62.5)	19 (61.3)	n.s.
	Gastric	4 (12.5)	3 (9.7)	
	Colorectal	3 (9.4)	4 (12.9)	
	Esophageal	5 (15.6)	5 (16.1)	
Stage	II (Esophageal cancer)	2 (6.3)	0 (0.0)	n.s.
	III	10 (31.3)	11 (35.5)	
	IV	19 (59.4)	18 (58.1)	
	Relapse	1 (3.1)	2 (6.5)	
Treatment	Chemotherapy	23 (71.9)	13 (41.9)	n.s.
	Chemotherapy+radiation	5 (15.6)	12 (38.7)	
	Other	4 (12.5)	6 (19.4)	
Use of the materials ^a				
	Read the material(s) prior to the consultation	24 (75.0)	23 (74.2)	n.s.
	Decided questions in advance	14 (43.8)	7 (22.6)	n.s.
	Wrote down questions in advance	2 (6.3)	0 (0.0)	n.s.
	Looked at the material(s) during the consultation	1 (3.1)	0 (0.0)	n.s.
	Checked physician's explanation with the material(s)	1 (3.1)	0 (0.0)	n.s.
	Asked questions included in the material(s)	6 (18.8)	1 (3.2)	n.s.

Proportions in the two groups were compared using Fisher's exact test or χ^2 test. Numerical scale was compared using the *t*-test.

^aBased on intention-to-treat analysis, four drop outs (intervention ($n = 2$); control group ($n = 2$)) were included in the analysis as 'nonuser'.

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prior to consultation. The mean usefulness rate of the material(s) in helping the patients to ask questions was significantly higher in the intervention group than in the control group (6.4 ± 2.3 and 3.4 ± 2.7 , respectively; $p < 0.001$; $t = 4.011$). The mean usefulness of the material(s) in helping the patients to understand the treatment plan was significantly higher in the intervention group than in the control group (6.5 ± 2.4 and 4.3 ± 2.5 , respectively; $p = 0.002$; $t = 3.215$). The mean score of willingness to use the material(s) in the future was significantly higher in the intervention group than in the control group (7.0 ± 2.6 and 3.5 ± 2.7 , respectively; $p < 0.001$; $t = 4.594$).

Satisfaction with the consultation

The levels of satisfaction with (1) the ability of the physician to answer the patients' questions, (2) asking questions, (3) understanding the condition of the disease, and (4) comprehending the treatment plan, as well as the overall level of satisfaction with the consultation were high in both groups, although not significantly different (Table 3).

Number and contents of the questions

We determined the estimated number of patient questions from patients' interview. Sixty-three percent of the patients in the intervention group and 71% of the patients in the control group asked question(s) during the consultation (no significant difference). Patients in both groups asked a median of 1.0 question (interquartile range, 2.0) (no significant difference). The majority of questions were related to information about treatment. The analysis

of the number of questions asked in each question category by the two groups showed no significant difference in any category.

Discussion

To our knowledge, this is the first study of evaluation of a QPS for advanced cancer patients deciding on their initial treatment. In addition, this is the first QPS study in Asia. Nearly half of the patients in the intervention group prepared questions prior to consultation (23% of the patients in the control group; no significant difference). We found that, compared with supplying the HIS only, advanced cancer patients who received both the HIS and the QPS rated the materials significantly more favorably with regards to the materials usefulness in helping them to ask questions of the physician and for future consultations. The results show similar findings to the previous study [8].

Unexpectedly, the use of the QPS did not seem to promote question-asking behavior. The total number of questions asked by the patients in the intervention group (median: 1.0) in the current study was, surprisingly, smaller than that in the intervention group in previous studies of patients seeing an oncologist for the first time (mean/median: 8.5–14.0) [6,8,15], although nearly half of the patients in the intervention group had decided on their questions in advance. Although we could not reliably compare the number of questions asked in the present study with that in previous studies (we did not audiotape the consultation as in previous studies), it appears that the patients in the current study asked fewer questions than those in the previous studies.

Table 2. Mean scores of usefulness of the material(s) ($n = 63$)

	Intervention ($n = 32$) Mean (SD)	Control ($n = 31$) Mean (SD)	<i>p</i> -Value
Usefulness of the material(s) in helping to ask questions	4.4 (3.6)	2.7 (2.8)	0.033
Usefulness of the material(s) in helping to understand the treatment plan	4.9 (3.6)	3.3 (2.8)	0.051
Willingness to use the material(s) in the future	5.3 (3.8)	2.8 (2.8)	0.006

SD, standard deviation. All items were rated on a 0–10 scale (e.g. 0 = completely disagree, 10 = completely agree). Scores in the two groups were compared using the *t*-test. Based on intention-to-treat analysis, four dropouts (intervention ($n = 2$); control group ($n = 2$)), 10 nonusers of the materials (intervention ($n = 6$); control group ($n = 4$)) and four partially missing (intervention ($n = 2$); control group ($n = 2$)) were included in the analysis as score '0'.

Table 3. Mean scores according to satisfaction with the consultation ($n = 63$)

	Intervention ($n = 32$) Mean (SD)	Control ($n = 31$) Mean (SD)	<i>p</i> -Value
Satisfaction with the ability of the physician to answer the patients' questions	8.1 (3.0)	8.2 (2.8)	0.893
Satisfaction with asking questions	6.8 (2.9)	7.8 (2.5)	0.177
Satisfaction with understanding the condition of the disease	8.0 (2.6)	8.2 (2.7)	0.810
Satisfaction with comprehending the treatment plan	8.1 (2.5)	7.8 (2.8)	0.665
Overall level of satisfaction with the consultation	7.9 (2.6)	7.8 (2.8)	0.847

SD, standard deviation. All items were rated on a 0–10 scale (e.g. 0 = completely disagree, 10 = completely agree). Scores in the two groups were compared using the *t*-test. Based on intention-to-treat analysis, four dropouts (intervention ($n = 2$); control group ($n = 2$)) were included in the analysis as score '0'.

We assume that one of the reasons behind the fewer questions in the current study was that the unique patient–physician relationship in Asian culture. The views in Asian countries on individuality and personal rights are distinctively different from those in North America and Western countries [16,17]. Watanabe *et al.* reported that Japanese cancer patients who felt that they were compelled to make a decision even though they had no sufficient information or understanding of their medical condition and treatment options were dissatisfied with the decision-making process [18]. Nomura *et al.* described the dominant category of patient–physician relationship in Japan as follows: ‘the relationship between a Japanese physician and a patient is clearly asymmetrical, since the patient seeks help and care from a medical expert whose diagnostic evaluations have to be accepted by the patient without discussion’ [19].

In Taiwan, the common practice of nondisclosure of prognosis and detailed disease-related information by healthcare professionals continues, although there is a need to disclose information on the medical condition of Taiwanese cancer patients [20]. Patient–physician relationships in Asian countries have traditionally been based on a paternalistic and hierarchical culture that discourages patients from questioning doctors. For this reason, cancer patients in Asian countries might need more intervention to make them feel comfortable to ask questions of their physicians. In the current study, we did not ask the physicians to refer to or endorse the QPS, however, considering the interactive nature of communication, a combination of QPS and active endorsement of QPS by physicians and/or communication skills training for physicians might be needed to promote question-asking behavior. Indeed, results from some previous studies suggest that physician endorsement of a QPS seems to enhance its effectiveness [3,7].

Overall ratings for the usefulness of the written materials were rather low. One possible reason is that a strict intention-to-treat analysis was conducted. The other possible reason is that we assigned a value of 0 for ratings of the usefulness of the written materials when they were not read by the participants. The rating of the QPS for those who read the materials were higher (range: 6.4–7.0).

In the current study, QPS was perceived by the patients as useful for helping them to ask relevant questions of their physician and for future use without an increase in the number of questions during the consultation. There are several possible explanations for this. First, Bruera *et al.* described that communication may be better when patients are able to ask their most meaningful questions rather than just more questions [8]. In the current study, patients in the intervention group might be able to consider the information they need to know in advance from QPS and thereby ask questions that better address their main concerns rather than

simply asking more questions. Second, QPS might be helpful in collecting and organizing information. Rainbird *et al.* reported that advanced cancer patients have high levels of unmet needs, particularly in the areas of psychological and medical communication/information [21,22]. Teno *et al.* reported that more than one-third of advanced cancer patients wanted more information about their test results at the time of diagnosis [23]. These previous studies indicate that advanced cancer patients experience difficulty in obtaining sufficient information during consultation. QPS may prove useful for advanced cancer patients in collecting and organizing information related to their medical condition. Finally, during the interview, some patients emphasized their expectations for the future use of QPS, since they had decided not to ask any questions in the first consultation because they believed that they must first listen to the physician’s explanation.

The level of satisfaction with the consultation was very high and there was no significant difference between the intervention group and the control group. Brown *et al.* reported that cancer patients rated their levels of satisfaction with the consultation extremely highly, even though their expectations were not met at the stated level desired [24]. Previous QPS studies also reported that the level of satisfaction showed a poor correlation with the number or duration of questions asked [14,15]. It might be difficult to evaluate the effect of QPS based on patients’ satisfaction levels with the consultation. Of note, although not a significant difference, the intervention group rated their satisfaction with asking questions (mean score of 6.8) less favourably than those in the control group (mean score of 7.8). Perhaps, the QPS raised patients’ expectations for being able to ask questions, and if the QPS was not endorsed or referred to by the physician then this caused the patient to be less satisfied with this aspect of the consultation.

Our study has several limitations. First, we could not get the required sample size because of dropout and research period restriction. Insufficient statistical power might lead underestimation. Second, we performed the study in only one cancer center and focused mainly on the first consultation. Thus, we cannot apply the present results to other settings and situations. The impact of the use of QPS over time and in other settings needs to be further examined in the future. Third, we did not audiotape the consultations and therefore were unable to analyze the consultations in detail. In some cases (intervention group ($n = 14$); control group ($n = 8$)), we timed the consultation length. For reference, the average consultation length showed no significant difference between the groups (31.1 ± 14.0 and 26.0 ± 12.2 , respectively; $p = 0.398$; $t = 0.864$). In addition, we interviewed patients and determined the estimated number of

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patient questions and the contents of questions, however, there is no evidence that patients' recall is accurate.

In conclusion, for those advanced cancer patients who read the QPS it seemed to be a moderately useful tool. Compared with controls, patients rated the QPS more favourably in terms of enabling them to ask relevant questions and for future use. The QPS seemed to help patients to prepare questions and it may help patients to articulate and organize their information needs. However, the QPS did not seem to directly promote patient confidence to ask questions. In Asian countries, active endorsement of QPS by physicians and/or communication skills training for physicians might be effective for promoting question-asking behavior. In the future, research

would be needed to examine the impact of the use of QPS over time and in other settings.

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Appendix A

Question Prompt Sheet is given in Table A1.

Table A1. Question prompt sheet

Diagnosis	1 What is the diagnosis?
	2 What is the stage of my cancer?
Condition of a disease	3 What is wrong with me?
	4 Where is my cancer located?
	5 Which test showed that?
Symptom	6 What symptoms will the cancer cause?
	7 What kind of treatments for the symptoms do you have?
Test	8 Do I need any more tests before my treatment?
	9 If so, does it hurt?
	10 What do the tests show?
Treatment	11 What treatment options are available for me?
	12 What are my options aside from anticancer drugs?
	13 What is the best case scenario? What is the worst case scenario? What is the most likely case scenario? How about survival length and quality of life?
	14 What complications, short/long side effects and sequelae does each treatment have?
	15 What is your recommendation regarding the best treatment for me?
	16 Which treatment do other patients with the same condition as mine choose?
	17 What is involved in administering the treatment, for example, contents, timing, frequency, duration, schedule, location, costs of treatments?
	18 What is the purpose of the treatment?
	19 What physical limitations will I have during the treatment?
	20 What are the common side effects of the treatment?
	21 Does the treatment cause pain?
	22 What can be done about the side effects?
	23 When will I know whether the treatment is working?
	24 How will I know whether the treatment is working?
	25 What are my next options if the treatment fails?
	26 What costs will I incur throughout my treatment?
	27 What is the percentage of success of this treatment for the other patients?
	28 Can I get my treatment at my local doctor's office?
	29 If I am taking alternative medicine, can I still continue?
	30 Can I take folk medicine or complementary and alternative medicine during treatment?
Life	13 Will the treatment affect my ability to work or perform other activities?
	32 Is there anything I have to do before and during my treatment?
	33 Is there anything I should not do during my treatment, for example, diet, exercise, housekeeping, sexual life, childbirth?
	34 Is it OK for me to do... during the treatment?
	35 Is it OK for me to eat/ drink... during the treatment?
	36 Is it OK for me to go...during the treatment?
	37 Is there anything that I should prepare before my treatment?
	38 What symptoms should I be alert for?
	39 What should I do when some symptoms occur?
Family	40 Will my family be affected by my cancer/ treatment?
	41 Will my family members have higher risk of getting cancer?
	42 Who can my family members talk to if they they have concern and worry?

Table A1. (Continued)

Psychological issues	43 Can I talk about my concern and worry?
	44 How can I cope with sleeplessness caused by anxiety and depressed feeling?
	45 Can you give me any advice on how to cope with the disease?
	46 Is there someone I can talk to about my feeling?
Prognosis	47 How long am I likely to live? The reason why I want to know is...
	48 Is there any chance for cure?
	49 What can I expect in the future?
Other issues	50 What causes cancer?
	51 How much time do I have to think about this? Do you need my decision today?
	52 There are some changes about... (in my life, physical aspect, mental aspect) after the previous consultation.
	53 The things that I hope to take precedence or continue doing in my life are...

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Brief report

Suicidal ideation among patients with gender identity disorder

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ABSTRACT

In this study, we tried to clarify the prevalence of suicidal ideation and self-mutilation including suicide attempts among patients with gender identity disorder (GID) and the relationship of those behaviors to demographic characteristics. A total of 500 consecutive Japanese GID patients without any other psychiatric comorbidity were evaluated at the outpatient GID Clinic of Okayama University Hospital. The lifetime rate of suicidal ideation was 72.0% of the total sample. There were no significant differences in the prevalence of suicidal ideation among groups divided by sex, age, age at onset or education. The lifetime prevalence of self-mutilation including suicide attempts was 31.8% of the total sample. Low level of education was significantly related to self-mutilation among both male-to-female and female-to-male GID patients. Younger age at onset was a significant factor affecting self-mutilation only among MTF GID patients. A lack of strategies to cope with severe distress among persons with lower education might induce a high frequency of self-mutilation including suicidal attempt. GID patients with a low level education might be at high risk of self-mutilation and should be watched with special attention to self-mutilation.

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1. Introduction

Gender identity disorder (GID) is characterized by a strong and persistent identification with the opposite sex and discomfort with one's own sex (American Psychiatric Association, 1994). Compared with many other psychiatric disorders, GID is rare, with an estimated worldwide lifetime prevalence of 0.001%–0.002% (Roberto, 1983) or 0.0019%–0.0024% (Landen et al., 1996a). The incidence of GID patients who requested sex reassignment therapy was reported to be 0.14/100,000/year in Sweden (Landen et al., 1996b). Thus, it has been difficult to establish demographic characteristics, and reports of large samples from countries outside of North America and Western Europe are extremely limited (Okabe et al., 2008; Matsumoto et al., 2009).

For most GID patients, a strong and persistent identification with the opposite sex and discomfort with one's own sex is a life challenge that often creates distress and carries potential stigmatization (Matsumoto et al., 2009; Hoshiai et al., 2010). Over half the GID patients experienced some form of harassment or violence within their lifetimes (Lombardi et al., 2001). Significantly more GID patients

reported suicide ideation and attempts than heterosexual males and females (Mathy, 2003; Clements-Nolle et al., 2006). Higher prevalence of suicidal ideation and suicide-related behaviors among GID patients might be due to societal oppression, stigmatization/discrimination and psychological mechanisms. However, there have been only a few studies on the prevalence of and risk factors for suicidal ideation and suicide-related behaviors among GID patients (Mathy, 2003; Clements-Nolle et al., 2006). The aim of the present study was to clarify the prevalence of and risk factors for suicidal ideation and self-mutilation including suicide attempt among GID patients in Japan.

2. Methods

2.1. GID clinic

The GID Clinic at Okayama University Hospital, the second oldest GID clinic in Japan, was established in Okayama in 1997. During the study period, the GID Clinic at Okayama University Hospital was the only special GID clinic in western Japan. It consists of four departments: psychiatry, urology, gynecology, and plastic and reconstructive surgery. The services at the GID Clinic include diagnosis, counseling, genetic testing, hormonal therapy, plastic surgery, and coordination of social services resources.

2.2. Ethics

This study was approved by the Internal Ethical Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences. After a complete description of the study to the subjects, written informed consent was obtained before their inclusion in the study.

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2.3. Subjects

A total of 603 consecutive Japanese patients consulted the outpatient GID Clinic of Okayama University Hospital between April 1, 1997, and October 31, 2005. All patients were comprehensively evaluated independently by at least two senior psychiatrists with a special interest in this area, and 579 of 603 patients fulfilled the criteria for GID according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association, 1994).

Of 579 GID patients, current psychiatric comorbidity was assessed independently by two senior psychiatrists according to several clinical interviews and clinical records. Current psychiatric comorbidity (Axis I) was diagnosed in 79 patients, and 500 patients were without psychiatric comorbidity. The relationship of psychiatric comorbidity to suicidal ideation and self-mutilation among GID patients was reported previously (Hoshiaki et al., 2010). To avoid the influence of current psychiatric comorbidity, only patients without psychiatric comorbidity were included in this study. All 500 patients were chromosomally and endocrinologically screened. Most patients were evaluated by psychological examinations including the stress coping inventory, the sentence completion test and the Baum test. The detailed results of the stress coping inventory were reported previously (Matsumoto et al., 2009). Statistical analyses on the results of other psychological tests have not been performed.

Of 500 patients, 311 (62.2%) were the female-to-male (FTM) type, and 189 (37.8%) were the male-to-female (MTF) type. The mean age at first examination was 26.4 ± 5.8 years for the FTM type, and 32.3 ± 10.6 years for the MTF type ($P < 0.001$; independent sample t-test, t value = -8.078 , degrees of freedom 498).

2.4. Suicidal ideation and self-mutilation

The lifetime presence or absence of serious suicidal ideation and self-mutilation was investigated by asking the following questions; "Have you ever seriously thought about committing suicide?" and "Have you ever mutilated yourself (including suicide attempt)?".

2.5. Statistics (data analysis)

Statistical analysis was conducted using SPSS 18.0 J (SPSS Inc., Chicago, IL, USA). The difference of the proportion of MTF and FTM GID patients among groups was evaluated using the χ^2 test. Comparison of suicidal ideation or self-mutilation for group differences was performed by the χ^2 test. The significance level was set at $P < 0.05$.

To identify which variables were significantly correlated with suicidal ideation or self-mutilation, we used multiple logistic regression. The multiple logistic regression analysis was performed using suicidal ideation or self-mutilation as a dependent variable. Independent variables were sex, age at first examination, age at onset (age when first thought about having the wrong sex), level of education, stage of therapy, steady partner and job. The final multiple logistic regression model was obtained after stepwise backward elimination of the independent variables using the likelihood-ratio test with $P < 0.10$. The strength of the relationship between independent variables and suicidal ideation or self-mutilation was expressed by means of an odds ratio (OR) with 95% confidence interval (CI) and P -value. Logistic regression analyses were conducted for MTF and FTM separately.

3. Results

3.1. Prevalence of suicidal ideation and self-mutilation (Table 1)

Demographic characteristics of the patients are shown at Table 1. The level of education was higher among MTF GID patients than among FTM GID patients. The presence of a steady partner was more frequent among FTM GID patients. Almost all variables differed between the MTF and FTM GID patients with the exception of suicidal ideation, self-mutilation and job.

Self-mutilation including suicide attempt was more frequent among GID patients with lifetime suicidal ideation; 43.3% among GID patients with lifetime suicidal ideation compared to 2.1% among GID patients without suicidal ideation. Almost all GID patients with a history of self-mutilation (97.9%) had experienced suicidal ideation.

3.2. Demographic characteristics of patients with suicidal ideation or self-mutilation

The prevalence rate of suicidal ideation was high in all age groups (Table 2). There were no significant differences in the prevalence rate of suicidal ideation among groups divided by age, age at onset, stage of therapy, level of education, steady partner or job (Table 2). Multiple logistic regression analysis revealed that younger age and higher stage

Table 1

Demographic characteristics of patients with gender identity disorder.

Variables	MTF	FTM	χ^2	P
<i>n</i>	189	311		
Age (years): <i>n</i> (%)				
-24	50 (26)	133 (42)		
25-29	30 (16)	98 (32)		
30-34	40 (21)	47 (15)		
35-	69 (37)	33 (11)		
mean age	32.3 ± 10.6	26.4 ± 5.8		<0.001
Age at onset: <i>n</i> (%)				
Before elementary school	54 (29)	219 (70)	119.508	<0.001
Lower grades of elementary school	27 (14)	47 (15)		
Higher grades of elementary school	29 (15)	24 (8)		
Junior high school	40 (21)	16 (5)		
Senior high school and thereafter	39 (21)	5 (2)		
Stage of therapy at first examination: <i>n</i> (%)				
No therapy	83 (44)	185 (60)	11.789	0.003
Hormonal therapy without genital surgery	73 (39)	91 (29)		
With genital surgery	33 (17)	35 (11)		
Level of education: <i>n</i> (%)				
University or higher	71 (38)	66 (21)	15.977	<0.001
High school	97 (51)	206 (66)		
Junior high school	21 (11)	39 (13)		
Steady partner: <i>n</i> (%)				
Present	68 (36)	198 (64)	36.194	<0.001
Absent	121 (64)	113 (36)		
Job: <i>n</i> (%)				
Employed	126 (67)	228 (73)	2.511	0.113
Unemployed	63 (33)	83 (27)		
Suicidal ideation: <i>n</i> (%)				
Positive	141 (75)	219 (70)	1.021	0.312
Negative	48 (25)	92 (30)		
Self-mutilation: <i>n</i> (%)				
Positive	60 (32)	99 (32)	0.000	0.984
Negative	129 (68)	212 (68)		

MTF, male-to-female type; FTM, female-to-male type.

Age at onset, Age at first thought about having the wrong sex.

of therapy at first examination were significantly affecting suicidal ideation among MTF GID patients (Table 3). On the other hand, there were no significant factors affecting suicidal ideation among FTM GID patients (Table 3).

Not a few GID patients among all age groups experienced self-mutilation including suicide attempt (25.5%–35.6%) (Table 4). There were no significant differences in the prevalence rate of self-mutilation among groups divided by age, age at onset, stage of therapy, steady partner or job (Table 4). The rate of self-mutilation was higher among GID patients with lower levels of education (50.0% among GID patients who completed junior high school, 34.3% among GID patients who completed high school, and 18.2% among GID patients who completed university or higher (Table 4). Multiple logistic regression analysis revealed that low level of education was significantly affecting self-mutilation among both MTF and FTM GID patients (Table 5). Younger age at onset was significant factors affecting self-mutilation only among MTF GID patients (Table 5).

4. Discussion

4.1. Suicidal ideation

For more than 10 years, the number of suicides in Japan has been over 30,000 in a population of 120,000,000. In addition, the suicide rate among Japanese has been shown to be higher than in other developed countries (Yoshimasu et al., 2006). Recently, Ono et al. reported that the lifetime prevalence estimates of suicidal ideation was 10.9% in Japan (Ono et al., 2008). On the other hand, Matsumoto et al. reported that the lifetime history of suicidal ideation of 1726 junior and senior high school students was 40.4% (Matsumoto et al., 2008).

Table 2
Comparison of GID patients with and without suicidal ideation.

Variables	Suicidal ideation		χ^2	P
	+	-		
n	360	140		
Age (years): n (%)				
-24	134 (37)	49 (35)	2.602	0.457
25-29	94 (26)	34 (24)		
30-34	65 (18)	22 (16)		
35-	67 (19)	35 (25)		
Age at onset: n (%)				
Before elementary school	196 (55)	77 (56)	1.386	0.847
Lower grades of elementary school	57 (16)	17 (12)		
Higher grades of elementary school	37 (10)	16 (11)		
Junior high school	40 (11)	16 (11)		
Senior high school and thereafter	30 (8)	14 (10)		
Stage of therapy at first examination: n (%)				
No therapy	189 (52)	79 (56)	0.627	0.731
Hormonal therapy without genital surgery	121 (34)	43 (31)		
With genital surgery	50 (14)	18 (13)		
Level of education: n (%)				
University or higher	92 (26)	45 (32)	2.722	0.256
High school	226 (62)	77 (55)		
Junior high school	42 (12)	18 (13)		
Steady partner: n (%)				
Present	192 (53)	74 (53)	0.009	0.924
Absent	168 (47)	66 (47)		
Job: n (%)				
Employed	247 (69)	107 (76)	2.980	0.084
Unemployed	113 (31)	33 (24)		

Among 73 GID patients, the lifetime prevalence of suicidal ideation was reported to be 37.0% (Mathy, 2003). Suicidal ideators among GID patients were more likely than non-ideators to report difficulties with alcohol and drugs (Mathy, 2003). In another study, half of the 163 MTF GID patients with sex reassignment surgery (SRS) had contemplated suicide in their lives before SRS (Imbimbo et al., 2009). We here clarify the high incidence rate of suicidal ideation among both MTF and FTM GID patients (MTF, 74.6%; FTM, 70.4%). The frequency is very high among all age groups or all patients grouped by age at onset or level of education. In the present study, GID patients with current psychiatric comorbidity were excluded. Therefore, the high frequency of suicidal ideation among GID patients cannot be explained by psychiatric comorbidity. However, we did not evaluate sub-threshold psychiatric symptoms. Over half the GID patients (239/402, 59.5%) experienced some form of harassment or violence within their lifetime (Lombardi et al., 2001). Sub-threshold depression and anxiety

Table 3
Multiple logistic regression analysis of factors affecting suicidal ideation.

	B	Standard error	P	Odds ratio	95% confidence interval of odds ratio	
					Lower	Upper
MTF						
Age	-0.038	0.016	0.020	0.963	0.932	0.994
Stage of therapy	0.579	0.263	0.027	1.785	1.067	2.986
Constant	1.358	0.604	0.025			
FTM						
Constant	0.867	0.124	0			

MTF, male to female type.

-2 log likelihood = 205.925; Model $\chi^2 = 8.270$ ($p = 0.016$).

Prediction equation: $p = 1/[1 + \exp(-1 \times \text{Score})]$.

Score = $-0.038 \times \text{Age} + 0.579 \times \text{Stage of therapy} + 1.358$.

FTM, female to male type.

Stage of therapy at first examination; No therapy = 1, Hormonal therapy = 2, With genital surgery = 3.

Table 4
Comparison of GID patients with and without self-mutilation.

Variables	Self mutilation		χ^2	P
	+	-		
n	159	341		
Age (years): n (%)				
-24	60 (39)	123 (37)	2.604	0.457
25-29	42 (26)	86 (25)		
30-34	31 (19)	56 (16)		
35-	26 (16)	76 (22)		
Age at onset: n (%)				
Before elementary school	90 (56)	183 (54)	6.594	0.159
Lower grades of elementary school	28 (18)	46 (13)		
Higher grades of elementary school	17 (11)	36 (11)		
Junior high school	17 (11)	39 (11)		
Senior high school and thereafter	7 (4)	37 (11)		
Stage of therapy at first examination: n (%)				
No therapy	79 (50)	189 (56)	2.061	0.357
Hormonal therapy without genital surgery	54 (34)	110 (32)		
With genital surgery	26 (16)	42 (12)		
Level of education: n (%)				
University or higher	25 (16)	112 (33)	21.655	<0.001
High school	104 (65)	199 (58)		
Junior high school	30 (19)	30 (9)		
Steady partner: n (%)				
Present	85 (53)	181 (53)	0.006	0.937
Absent	74 (47)	160 (47)		
Job: n (%)				
Employed	111 (70)	243 (71)	0.110	0.740
Unemployed	48 (30)	98 (29)		

might influence the high prevalence rate of suicidal ideation among GID patients.

Younger age and higher stage of therapy at first examination were associated with suicidal ideation among MTF GID patients in the present study. Younger age was reported to be significantly associated with the prevalence of suicidal attempt among GID patients (Clements-Nolle et al., 2006). GID patients at younger age may be vulnerable to gender-based harassment. MTF GID patients with hormonal therapy and/or genital surgery showed a higher prevalence of suicidal ideation in our study. More severe distress with suicidal ideation may induce a strong desire and real actions to receive a higher stage of therapy. However, we cannot clarify why younger age

Table 5
Multiple logistic regression analysis of factors affecting self mutilation.

	B	Standard error	P	Odds ratio	95% confidence interval of odds ratio	
					Lower	Upper
MTF						
Level of Education	-0.966	0.268	0.000	0.381	0.225	0.643
Age at onset	-0.336	0.114	0.003	0.714	0.572	0.893
Constant	2.296	0.710	0.001			
FTM						
Level of Education	-0.677	0.223	0.002	0.508	0.328	0.786
Constant	0.625	0.464	0.179			

MTF, male to female type.

-2 log likelihood = 213.842; Model $\chi^2 = 22.386$ ($p < 0.001$).

Prediction equation: $p = 1/[1 + \exp(-1 \times \text{Score})]$.

Score = $-0.966 \times \text{Level of education} - 0.336 \times \text{Age at onset} + 2.296$.

FTM, female to male type.

-2 log likelihood = 379.407; Model $\chi^2 = 9.718$ ($p = 0.002$).

Prediction equation: $p = 1/[1 + \exp(-1 \times \text{Score})]$.

Score = $-0.677 \times \text{Level of education} + 0.625$.

Level of education; Junior high school = 1, High school = 2, University of higher = 3.

Age at onset; Before elementary school = 1, Lower grades of elementary school = 2.

Higher grades of elementary school = 3, Junior high school = 4, Senior high school and thereafter = 5.

and higher stage of therapy were related to prevalence of suicidal ideation, only among MTF/GID patients.

4.2. Self-mutilation

The prevalence of suicidal attempt among 515 GID patients was reported to be 32% (MTF, 32%; FTM, 32%) (Clements-Nolle et al., 2006). Younger age (<25 years), depression, substance abuse treatment, forced sex, gender-based discrimination, and gender-based victimization were independently associated with suicidal attempt (Clements-Nolle et al., 2006). In another study, the lifetime prevalence of suicidal attempt was reported to be 23.3% among 73 GID patients (Mathy, 2003). Attempters were more likely than non-attempters to report psychiatric medications as well as difficulties with alcohol and/or drugs (Mathy, 2003). The prevalence of suicidal ideation and suicidal attempt among GID patients was reported to decrease dramatically after SRS (Imbimbo et al., 2009).

In this study, the prevalence rate of self-mutilation including suicide attempt was high among both MTF and FTM GID patients (31.7% in MTF, and 31.8% in FTM GID patients), and similar to that in the study by Clements-Nolle et al. However, in this study, the presence or absence of forced sex, gender-based discrimination and gender-based victimization was not estimated. GID patients with psychiatric comorbidity were not included. Therefore, most of the risk factors reported in their study could not be assessed.

The prevalence rate of self-mutilation was higher among GID patients with less education. Multiple logistic regression analysis revealed that low level of education was a significant factor affecting self-mutilation. The intimate relationship of low level education to suicidal attempt was reported (Ozdel et al., 2009; Tang et al., 2009). The majority of suicide attempters were characterized by low educational status (Ozdel et al., 2009), and dropout from school was associated with suicidal attempt (Tang et al., 2009). A lack of strategies to cope with severe distress among persons with lower education might induce a high frequency of self-mutilation including suicidal attempt (Ozdel et al., 2009; Tang et al., 2009). In GID patients with a low education level, special attention should be paid to the possibility of self-mutilation.

Besides low level of education, younger age at onset was independently associated with self-mutilation among MTF/GID patients. Severe distress in childhood might influence the prevalence of self-mutilation (Tang et al., 2009). However, we cannot clarify why younger age at onset was related to prevalence of suicidal ideation, only among MTF/GID patients.

4.3. Limitation of this study

Several limitations of this study have to be considered. Firstly, it is a clinic-based study rather than a field study. Therefore, the sample is large, but not necessarily representative of all GID individuals. As stated above, in this study, 60.3% were FTM GID patients, and 39.7% were the MTF type. This proportion is not common in studies on GID. Secondly, the data were based on retrospective self-reporting of the occurrence and timing of suicide-related outcomes and mental disorders, and thus may be subject to underreporting and biased recall. We could not collect information from third-party informants to validate the respondents' reports. Thirdly, we were unable to clarify the frequency of self-mutilation. Therefore, for example, GID patients

reporting self-mutilation include both those with only one instance of self-mutilation and frequent self-cutters. Fourth, psychiatric comorbidity was diagnosed according to DSM-IV, but the structured interview for DSM-IV was not used. Regarding the results of Hepp et al. (2005) who found a comorbidity rate of 39% (12/31) using the structured clinical interview, a comorbidity rate of 14% (79/579) in this study was low. The possibility that clinical diagnosis without a structured interview missed psychiatric comorbidity cannot be denied. Further investigation is needed to clarify in more detail the relationship of suicidal ideation and self-mutilation to various risk factors.

Despite these limitations, this is the first report to clarify the prevalence of and risk factors for suicidal ideation and self-mutilation including suicide attempt among GID patients outside of North America and Western Europe.

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Kana Pick-out Test and brain perfusion imaging in Alzheimer's disease

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ABSTRACT

Background: The Kana Pick-out Test (KPT), which was developed in Japan, is suitable for evaluating frontal lobe function and screening for mild dementia. However, the neural substrates involved remain to be elucidated. The aim of the present study was to identify the regional perfusion patterns in the brain associated with performance scores on the KPT in patients with mild Alzheimer's disease (AD), using brain perfusion assessed by single photon emission computed tomography (SPECT).

Methods: Twenty AD patients with high scores on the KPT and 20 age- and sex-matched AD patients with low scores were selected from 227 consecutive Japanese patients of the Memory Clinic of Okayama University Hospital. All 40 subjects underwent brain SPECT with 99mTc-ethylcysteinate dimer, and the SPECT images were analyzed by Statistical Parametric Mapping.

Results: With the exception of KPT scores, no significant differences were found between high and low scoring groups with respect to Addenbrooke's Cognitive Examination scores, Mini-mental State Examination scores, or the depression score of the Neuropsychiatric Inventory subscale. Compared to patients with high scores on the KPT, AD patients with low scores on the KPT showed significant hypoperfusion in the left subgenual cingulate gyrus (SGC) extending to the right SGC.

Conclusions: Our results suggest that functional activity of the SGC is closely related to scores on the KPT. KPT might be a promising strategy to use in detecting early stages of AD with low SGC function.

Key words: Alzheimer's disease (AD), cerebral blood flow (CBF), Kana Pick-out Test (KPT), single photon emission computed tomography (SPECT), Statistical Parametric Mapping (SPM)

Introduction

The Kana (Japanese syllabogram) Pick-out Test (KPT) was developed to evaluate frontal lobe function easily and quickly at the bedside (Kaneko, 1996). The test is said to be suitable for inspecting higher-order brain function and to be a good method for screening persons with mild or slight dementia (Inoue *et al.*, 2003). Although the clinical usefulness of the KPT in dementia is well documented, the neural substrates involved remain unclear. There are few functional neuroimaging studies investigating brain regions related to the KPT performance of dementia patients (Nakatsuka

et al., 2003; Tachibana *et al.*, 2007). In the present study we investigated the relationship of KPT scores to regional cerebral blood flow (rCBF) in order to assess the neural substrates of KPT performance in patients with mild Alzheimer's disease (AD).

In most neuroimaging studies in which rCBF was evaluated, stereotaxic analysis of regions of interest (ROIs) was used. However, the reproducibility and objectivity of the results are controversial because small ROIs were manually placed on selected slices of single photon emission computed tomography (SPECT) images of the patient. Image analysis using ROIs has been criticized for the serious shortcoming that any information outside of the ROIs is not obtained. To overcome the above disadvantages, in the present study we conducted an evaluation using statistical parametric mapping (SPM) comparison which has the advantage of making no a priori anatomical hypotheses.

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Methods

Kana pick-out test

In the KPT, the subjects are shown a short story written in Japanese kana characters. The original paper version on which a short story is written in Japanese kana characters was described previously (Inoue *et al.*, 2003). The subjects are required to find as many vowel symbols as possible within two minutes, while understanding the meaning of the story (Kaneko, 1996; Nakatsuka *et al.*, 2003). While reading the story, the subjects circle the vowel symbols with a pencil. If the subjects concentrate only on reading the story, they tend to become careless in finding the symbols. Inversely, if they concentrate on finding the symbols, they tend to forget the substance of the story. Thus, this test assigns two simultaneous tasks: find the vowel symbols and recognize the content of the story (Inoue *et al.*, 2003). The Japanese kana character set consists of 66 phonetic symbols that include five vowels; the story consists of 406 symbols with 61 vowels, so the full score for this test is 61. The lower normal limits of KPT scores are 11 for those in their seventies, 10 for those in their eighties, and 9 for those in their nineties (Kaneko, 1996). In this study, the subjects with low scores on the KPT did not reach the lower limits of normal, and the subjects with high scores on the KPT were required to score higher more than the mean score for their ages (20 for those in their 60s, 18 for those in their 70s, and 16 for those in their 80s) (Kaneko, 1996).

In this study, KPT memory score was also recorded. Two questions to examine whether the subjects remembered the substance of the story were asked, and the memory score was determined according to the following criteria: 10 for two correct answers, 5 for one correct answer (full score was 10).

Subjects

Twenty AD patients with a dementia severity of 0.5 (possible) or 1 (mild) based on the Clinical Dementia Rating (CDR) (Hughes, *et al.*, 1982), whose score on the KPT did not reach the lower limits of normal, were selected from 227 consecutive Japanese patients who were fully examined at the Memory Clinic of Okayama University Hospital, between April 2004 and March 2008. Thereafter, 20 AD patients with high scores on the KPT, matched for age, sex ratio, education, and scores on the Addenbrooke's Cognitive Examination (ACE) (Mathuranath *et al.*, 2000; Yoshida *et al.*, 2010), were also selected.

The inclusion criteria for all participants were: (i) they underwent general physical and neurological

examinations and extensive laboratory testing, including thyroid function tests, serum vitamin B12, and syphilis serology; (ii) they took the KPT, Mini-mental State Examination (MMSE) (Folstein *et al.*, 1975) and ACE; (iii) underwent brain SPECT as well as head CT and/or head MRI; (iv) they were diagnosed with probable AD according to the NINCDS-ADRDA criteria (McKhann *et al.*, 1984); (v) they had a dementia severity of 0.5 or 1 based on the CDR (Hughes, *et al.*, 1982); and (vi) they or their nearest relatives gave informed written consent. The exclusion criteria were (i) complications from other neurological diseases or illnesses; (ii) history of mental illness or substance abuse prior to the onset of dementia; (iii) any evidence of focal brain lesions on head MRI; (iv) treatment with cholinesterase inhibitors, antipsychotics, antidepressants or anxiolytic drugs; and (v) left-handedness or ambidexterity. The profile of each participant (age, sex, years of education, and disease duration) was recorded, and the CDR score was rated by the chief clinician.

Other instruments

Addenbrooke's Cognitive Examination (ACE) was developed to provide a brief test sensitive to early stage dementia, and is capable of differentiating between dementia subtypes including AD, fronto-temporal dementia, progressive supranuclear palsy and other parkinsonian syndromes (Mathuranath *et al.*, 2000). ACE includes the MMSE but extends it to encompass important areas not covered by the MMSE, such as frontal-executive function and visuospatial skills. ACE has a comparable sensitivity to the Dementia Rating Scale (Bak *et al.*, 2005), a well-established dementia screening tool, widely used in research but not in clinical practice because of its length and difficulty of administration. For this study, we used the Japanese version of ACE described by Yoshida *et al.* (2010). The reliability of the Japanese version of ACE is excellent, and its validity is, to some extent, established (Yoshida *et al.*, 2010).

The Physical Self-Maintenance Scale (PSMS) and the Instrumental Activities of Daily Living scale (IADL) are validated scales for the assessment of activities of daily living (ADL) (Lawton and Brody, 1969; Hokoishi *et al.*, 2001). The PSMS is a six-item scale that rates self-care ability in toileting, feeding, dressing, personal hygiene and grooming, locomotion (physical ambulation), and bathing. The IADL scale assesses patients' ability to perform eight complex daily tasks: ability to use the telephone, shopping, food preparation, household tasks, laundering, mode of transportation, responsibility for medications, and ability to manage finances.

The Neuropsychiatric Inventory (NPI) is a valid and reliable instrument for measuring behavior in dementia (Cummings *et al.*, 1994; Hirono *et al.*, 1997). It is a caregiver-based tool that assesses ten common behaviors in dementia.

Ethics

This study adhered to the 1975 Helsinki Declaration of Human Rights and the study protocol was approved by the Committee of Okayama University Hospital on Human Research. After providing a complete description of the study to the subjects and their relatives, written informed consent was obtained.

Brain perfusion SPECT imaging

All subjects were examined by brain perfusion SPECT. Patients were examined in a comfortable supine position with their eyes closed in quiet surroundings. First, the passage from the heart to the brain was monitored after intravenous administration of ^{99m}Tc -ethylcysteinate dimer (ECD, 600 MBq, Daiichi Radioisotope Laboratories Ltd., Tokyo, Japan). Ten minutes after the angiography, SPECT images were obtained using a triple-head, rotating gamma camera interfaced to a minicomputer (GCA9300A/DI; Toshiba, Tokyo, Japan) equipped with a fanbeam, low-energy, high-resolution collimator. Sixty projection images over a 360° angle in a 128×128 matrix were acquired. All images were reconstructed using ramp-filtered back-projection and then three-dimensionally smoothed with a Butterworth filter (order 8, cutoff 0.12 cycles/cm). The reconstructed images were corrected for gamma ray attenuation using the Chang method ($\mu = 0.09$).

Data analysis

Spatial reprocessing and statistical analysis of images was performed on a voxel-by-voxel basis using Statistical Parametric Mapping 2 (SPM2, Wellcome Department of Imaging Neuroscience, U.K.) running on MATLAB (The Mathworks, Inc). All SPECT images of each subject were normalized to the standard brain of the Montreal Neurological Institute (MNI), and the spatial normalization was performed with 12-parameter affine and non-linear transformations (Friston *et al.*, 1995a; 1995b). The voxel sizes of the reslice option were (2 mm, 2 mm, 2 mm). The non-linear parameter was set at 25 mm cut-off basis functions and 16 iterations. All of the normalized SPECT images were then smoothed with an isotropic gaussian kernel filter (12-mm full-width at half-maximum). To examine the images for specific regions showing differences in perfusion, two sample *t*-tests were

performed. Global normalization was performed by proportional scaling with the mean voxel value. Masking was applied using the threshold method (0.8 times the global value). The statistical height threshold was set at $P < 0.005$ uncorrected, and the extent threshold was set at $P < 0.01$ with correction for multiple non-independent comparisons.

Statistical analysis

Statistical analysis was performed using the SPSS 14.0J software program (SPSS Inc., Chicago, IL). Comparisons between the two groups were performed by independent sample *t*-tests. A value of $p < 0.05$ was accepted as significant.

Results

Age, years of education, duration of illness, neuropsychological test scores and ADL

No significant differences were found between high- and low-score groups with respect to age, years of education, or duration of disease by Student's *t*-test (Table 1). With the exception of KPT scores, no significant differences were found between high- and low-score groups with respect to ACE scores, MMSE scores, KPT memory scores or NPI subscale scores (Tables 1 and 2).

Comparison on ADL scales revealed that AD patients with a low KPT score got lower scores than those with a high KPT score, in the total scores of PSMS and the subscale scores of dressing, physical ambulation, shopping and responsibility for own medications among PSMS and IADL (Table 2).

rCBF

A group comparison of the SPM results between the high- and low-score groups were performed. Specific voxels with a significantly lower perfusion in the low-score group than in the high-score group are shown in Figure 1 and Table 3. A similar test for specific voxels with a significantly lower perfusion in the high-score group than in the low-score group found no cluster of voxels.

Figure 1 shows the z-score for each voxel in this cluster superimposed onto a three-way-glass brain view. It shows a significant cluster of voxels in the left subgenual cingulate gyrus (SGC), extending to right SGC. Table 3 shows the probability results of the SPM analysis and the location of peak z scores in terms of the MNI coordinates.

Discussion

Kana Pick-out Test score and rCBF

The KPT is a popular test of attention in Japan. This task requires parallel processing of

Table 1. Clinical characteristics and neuropsychological tests

GROUP	LOW SCORE	HIGH SCORE	T	P
Total (n)	20	20		
Sex (n) (male/female)	7/13	7/13		
Age (mean years \pm S.D.)	74.2 \pm 6.1	74.3 \pm 6.5	0.075	0.940
Education (mean years \pm S.D.)	11.1 \pm 2.7	11.0 \pm 2.7	-0.059	0.953
Duration of disease (mean years \pm S.D.)	2.8 \pm 2.5	2.6 \pm 2.0	0.284	0.778
ACE score (mean \pm S.D.)	62.5 \pm 7.6	63.5 \pm 8.6	0.409	0.685
MMSE score (mean \pm S.D.)	22.1 \pm 1.8	21.6 \pm 2.3	-0.851	0.400
KPT score (mean \pm S.D.)	4.8 \pm 2.7	25.2 \pm 6.1	13.657	0.000
KPT memory score (mean \pm S.D.)	2.8 \pm 3.0	4.0 \pm 3.8	-1.144	0.260

Low score = Alzheimer's disease patients with low score on Kana Pick-out Test.

High score = Alzheimer's disease patients with high score on Kana Pick-out Test.

ACE = Addenbrook's cognitive examination; MMSE = Mini-mental State Examination.

KPT = Kana Pick-out Test; S.D. = Standard Deviation.

Table 2. Activities of daily living (ADL) and instrumental ADL

GROUP	LOW SCORE	HIGH SCORE	T	P
Neuropsychiatric Inventory (mean \pm S.D.)				
Delusion	1.4 \pm 3.4	2.1 \pm 3.6	0.630	0.532
Hallucination	0.8 \pm 2.7	0.3 \pm 0.9	-0.787	0.436
Agitation/Aggression	1.2 \pm 2.3	2.0 \pm 3.2	0.910	0.368
Depression	1.3 \pm 3.1	1.7 \pm 3.0	0.362	0.719
Anxiety	1.3 \pm 1.9	2.2 \pm 3.3	1.065	0.294
Euphoria	0.4 \pm 1.2	0.5 \pm 1.2	0.128	0.899
Apathy	4.9 \pm 4.4	2.9 \pm 3.5	-1.618	0.114
Disinhibition	1.3 \pm 3.2	1.9 \pm 3.1	0.649	0.520
Irritability	0.9 \pm 2.2	2.0 \pm 3.1	1.291	0.204
Aberrant motor behavior	0.6 \pm 2.0	0.0 \pm 0.0	-1.371	0.178
PSMS (mean \pm S.D.)	4.6 \pm 1.3	5.7 \pm 0.7	3.183	0.003
Toilet	0.9 \pm 0.4	1.0 \pm 0.0	1.831	0.075
Feeding	1.0 \pm 0.0	1.0 \pm 0.0	0.000	1.000
Dressing	0.8 \pm 0.4	1.0 \pm 0.0	2.179	0.036
Grooming	0.7 \pm 0.5	0.9 \pm 0.3	1.934	0.061
Physical ambulation	0.4 \pm 0.5	0.8 \pm 0.4	2.757	0.009
Bathing	0.9 \pm 0.3	1.0 \pm 0.2	0.588	0.560
IADL (mean \pm S.D.)	4.7 \pm 2.2	5.8 \pm 1.7	1.857	0.071
Ability to use telephone	0.9 \pm 0.3	1.0 \pm 0.0	1.453	0.154
Shopping	0.4 \pm 0.5	0.7 \pm 0.5	2.307	0.027
Food preparation	0.4 \pm 0.5	0.4 \pm 0.5	0.000	1.000
Housekeeping	0.9 \pm 0.4	1.0 \pm 0.0	1.477	0.153
Laundry	0.8 \pm 0.4	1.0 \pm 0.0	1.897	0.070
Mode of transportation	1.0 \pm 0.0	1.0 \pm 0.0	0.000	0.216
Responsibility for own medications	0.4 \pm 0.5	0.6 \pm 0.5	1.258	0.038
Ability to handle finances	0.7 \pm 0.5	1.0 \pm 0.2	2.147	0.071

Low score = Alzheimer's disease patients with low score on Kana Pick-out Test.

High score = Alzheimer's disease patients with high score on Kana Pick-out Test.

PSMS = Physical Self-Maintenance Scale; IADL = Instrumental Activities of Daily Living scale.

S.D. = Standard Deviation.

reading and picking out letters, and demands an appropriate allocation of attentional resources to the two activities. Therefore, the KPT is thought to be a suitable test of working memory and executive function (Tamura *et al.*, 2003), and to reflect prefrontal area function (Tachibana *et al.*, 2007).

There have been only a few studies of the relationship between results of the KPT and rCBF (Nakatsuka *et al.*, 2003; Tachibana *et al.*, 2007). At a memory clinic, the mean rCBF among four outpatients whose MMSE score was normal but whose KPT scores were abnormal was reported to be decreased in the posterior cingulate gyrus

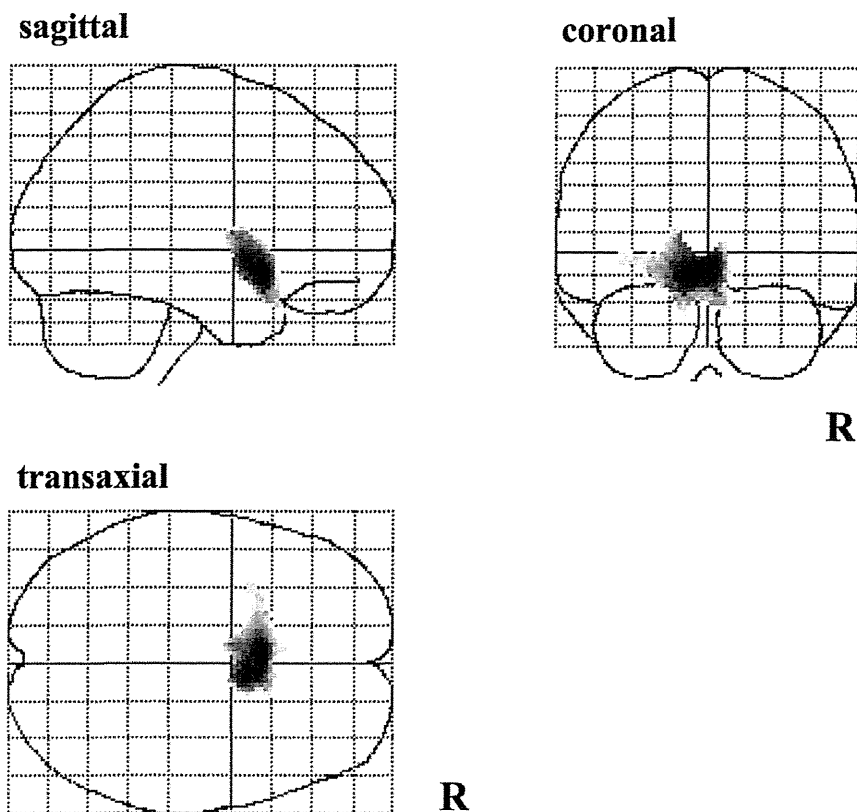


Figure 1. SPM (z) map of rCBF decrease in AD patients with low scores on the Kana Pick-out Test compared with AD patients with high scores. Three-way-glass view of the area of significant hypoperfusion.

Table 3. Significant regional uptake differences between AD patients with low and high scores on Kana Pick-out Test (KPT)

DIRECTION OF DIFFERENCE	NUMBER OF VOXELS	PEAK Z SCORES	COORDINATES (MNI)		
			X	Y	Z
Decrease uptake in AD patients with low scores on KPT	1199	3.58	-8	16	-12
		3.49	4	14	-10
		3.15	-14	14	-6

AD = Alzheimer's disease; MNI = Montreal Neurological Institute.

and cinguloparietal transitional area, compared to the mean rCBF among four cases in which both the MMSE and the KPT scores were normal (Nakatsuka *et al.*, 2003). A functional MRI (fMRI) study of the four cases showed significant increases in blood oxygenation level-dependent signals in the prefrontal area, sensorimotor area, parietal association area, and visual cortex during performance of the computerized KPT (Tachibana *et al.*, 2007). Inconsistent with these two previous findings, we found rCBF in the bilateral SGC was decreased in AD patients with low scores on the KPT compared with AD patients with high scores.

The results of the three reports, including our own, were different from each other. What caused the differences? There are two major differences among the three studies. The first is a difference in the diseases. All subjects in the study by Tachibana *et al.* (2007) were cognitively normal subjects, whereas subjects in the other two studies were memory clinic outpatients. All eight cases in the study by Nakatsuka *et al.* (2003) were patients with subjective complaints of forgetfulness, but all eight cases showed normal MMSE scores. In our study, all 40 subjects were patients with AD, and the mean MMSE scores were 22.1 among patients with low

KPT scores and 21.6 among patients with high KPT scores.

The second was the difference in the methods of evaluating brain function. Tachibana *et al.* (2007) used fMRI, whereas the other two studies used brain SPECT. In the study by Nakatsuka *et al.* (2003), ^{99m}Tc-hexamethyl-propyleneamine oxine was injected intravenously, and the z-value, which shows the distance from the mean, was calculated by three-dimensional stereotactic surface projections (3D-SSP). Thus, the exact rCBF was not calculated, and deep brain structures such as the basal ganglia and thalamus were not evaluated. In this study, ^{99m}Tc-ECD was used, and rCBF was compared using SPM. The difference of patients and methods among three studies, we suppose, might influence the difference in results.

In addition, the number of participants in the three studies was different. In Nakatsuka's study, four subjects with low KPT scores were compared with another four subjects with normal KPT scores (Nakatsuka *et al.*, 2003). In Tachibana's study, four cases were examined with fMRI (Tachibana *et al.*, 2007). In this study, 20 subjects with low KPT scores were compared with 20 subjects with high KPT scores. The number of the participants in this study was larger than those of previous studies, which we believe is an advantage of this study.

Subgenual cingulate gyrus

The extensive interconnections between the posterior SGC and the nucleus tractus solitarius of the vagus led to this region initially being termed the "visceromotor cortex" (Drevets *et al.*, 2008), and the SGC is thought to be involved in autonomic conditioning functions (Vogt, 2005). At the same time, the SGC has been implicated in the modulation of emotional behavior on the basis of neuroimaging studies in humans (Drevets *et al.*, 2008). The SGC is activated during sad events (Vogt, 2005), and the mean gray matter volume of the SGC is abnormally reduced in subjects with mood disorders, irrespective of mood state (Drevets *et al.*, 2008). Moreover, a preliminary report in six patients suggested that deep brain stimulation of the SGC may provide a benefit in treatment-resistant depression (Lozano *et al.*, 2008).

The SGC is a very important area for mood disorder as stated above. Therefore, it is, of course, possible that a depressive mood affects the results of the KPT, and that a depressive mood among patients with AD causes both the low scores of KPT and hypoperfusion in the subcallosal area. However, in this study, depression scores in NPI did not differ between high- and low-score groups. Therefore, we

believe that the relationship between low scores on the KPT and low perfusion in the SGC was not mediated by depressive mood.

The SGC has been implicated in the tracking of reward value (Rolls, 2000; 2004), and disinhibition in frontotemporal dementia showed unique associations with tissue loss in the SGC (Rosen *et al.*, 2005). The SGC possesses significant connections with the orbitofrontal cortex and amygdala (Doyon *et al.*, 1996), with the ventral striatum (Baker *et al.*, 1996), and with other limbic structures (Dupont *et al.*, 1994). Lesion of the SGC was reported to lead to impaired decision-making based on future consequences (Bechara *et al.*, 1994). The alterations of rCBF in the SGC could affect those neuronal networks related to executive functions, and correlate with scores of the KPT in mild AD. Our results suggest that functional activity of the subcallosal area is closely related to the score on the KPT. KPT might be a promising strategy to use for detection of the early stages of AD with low SGC function.

Significant metabolic decrease in specific medial prefrontal areas, namely the SGC and the anterior cingulate cortex, are reported to be initiated early in the course of AD (Fouquet *et al.*, 2009). In support of this contention, the same two medial prefrontal areas showed specific perfusion decrease from the entorhinal to the limbic neuropathologic Braak stages (Braak and Braak, 1991), corresponding to amnesic mild cognitive impairment and early AD, respectively (Bradley *et al.*, 2002).

KPT and ADL

The KPT was developed to evaluate frontal executive function easily and quickly at the bedside (Kaneko, 1996; Inoue *et al.*, 2003). It has been reported that a range of deficits in executive functioning adversely affect the ability of AD patients to perform ADL (Njegovan *et al.*, 2001; Feldman *et al.*, 2001). In this study, AD patients with low scores on the KPT showed lower scores than those with high scores on the KPT in the total score of PSMS and the subscale scores of dressing, physical ambulation, shopping and responsibility for own medications among PSMS and IADL. Our results suggest that performance on the KPT is closely related to several ADL as well as rCBF in the SGC, independently of ACE and MMSE scores.

Limitation of this study

Our study has several limitations. The participants in this study consisted of patients with mild AD who were recruited at a university center. Thus,