PATIENTS AND METHODS

Contents of Survey

Survey questions were drawn up after a review of pertinent literature. A panel of experts including consultation-liaison psychiatrists, psychosomatic physicians, psychologists, nurses and palliative care specialists reviewed and revised the survey before distribution (4,19,30,31). Survey questions were generated based on the tripartite division of quality assessment and monitoring: structure, processes and outcomes to evaluate the clinical aspects of consultation-liaison psychiatry in palliative medicine (32). The questionnaire consisted of multiple-choice, Likert-scale and fill-in questions.

The questionnaire focused on six areas, which included hospital characteristics, professional backgrounds, clinical activities, availabilities, processes of practice and educational activities. Specific attention was paid to consultation processes: assessing physical and psychosocial symptoms, assessing decision-making capacities, assisting with decision-making regarding treatment, establishing the goals of care, interacting frequently with physicians and staff, coordinating care across providers and providing appropriate follow-up.

Subjects

Cancer Hospitals

The designated cancer hospitals in Japan were identified from the database of the Center for Cancer Control and Information Services at the National Cancer Center and the list published by the Office for Cancer Control, Health Services Bureau, Ministry of Health, Labour and Welfare.

We obtained a list of 375 government-designated cancer hospitals, which provide services to ~25% of the cancer patients in Japan. At 90 of the designated cancer hospitals, the palliative care teams were approved for national medical insurance. We surveyed all government-designated cancer hospitals.

We identified the consultation-liaison psychiatrists (in some centers, psychosomatic physicians on behalf of psychiatrists) of 375 government-designated cancer hospitals from the database of the Center for Cancer Control and Information Services at the National Cancer Center and verified those who were core members of the palliative care teams through personal telephone contact with the cancer care support center of each institution.

Survey Process

Survey questionnaires were sent to the 375 government-designated cancer hospitals, asking the team psychiatrists and psychosomatic physicians about their programs and clinical activities. The initial invitation was included with the mail survey. Recipients were given 6 weeks to complete the questionnaire anonymously and return it by mail. A reminder letter was sent to non-respondents at 6 and 12 weeks. Data collection was performed between November 2009 and February 2010.

Statistical Analysis

We summarized the availability and the characteristics of psychiatric consultation-liaison services involved with the palliative care teams by using standard descriptive statistics, including medians, interquartile ranges (IQRs), proportions and frequencies, together with 95% confidence intervals where appropriate. Differences in services provided between the approved and non-approved palliative care teams were evaluated using Fisher exact tests for categorical variables. The Mann–Whitney test was used for non-parametric continuous variables. $P < 0.05$ was considered statistically significant. SPSS version 17.0 software (SPSS Inc., Chicago, IL) was used for statistical analyses.

RESULTS

Of the 375 questionnaires that were mailed, 243 were returned (response rate = 64.8%). Of these, 10 were excluded due to missing data for the primary end points. Thus, 233 responses were finally analyzed (effective response rate = 62.1%). Psychiatrists and psychosomatic physicians of the approved palliative care teams were more likely to respond compared with those of the non-approved palliative care teams (88.8 versus 53.7%).

Characteristics of Consultation-liaison Psychiatrists and Psychosomatic Physicians at Designated Cancer Hospitals

Table 1 shows the background characteristics of consultation-liaison psychiatrists and psychosomatic physicians, infrastructure for psychiatry and palliative care, and structure of palliative care teams at designated cancer hospitals. The years of clinical experience of psychiatrists at cancer hospitals with approved palliative care teams was shorter than those with non-approved palliative care teams [16.3 versus 18.8 (years); $P < 0.02$]. On the other hand, the rate of psychiatrists of approved palliative care teams taken part in the government-certified palliative care workshop was higher than that of non-approved palliative care teams (90 versus 77%; $P < 0.02$).

Compared with the cancer hospitals with non-approved palliative care teams, those with approved palliative care teams were significantly more likely to have full-time psychiatrists and psychiatric outpatient services. All cancer hospitals with approved palliative care teams involved psychiatric consultation-liaison services. On the other hand, the rate of integration of services was only 73% at cancer hospitals with non-approved palliative care teams.

The number of inpatient beds was higher at cancer hospitals with approved palliative care teams compared with those

Table 1. Characteristics of consultation-liaison psychiatrists and psychosomatic physicians at designated cancer hospitals

	Cancer hospitals with approved palliative care teams ($n = 80$)	Cancer hospitals with non-approved palliative care teams ($n = 153$)	*P*-value
Professional background of psychiatrists and psychosomatic physicians on palliative care team			
Clinical experience (years)	16.3 (±6.9)	18.8 (±8.0)	0.02
Clinical experience in cancer care (years)	7.9 (±6.8)	7.0 (±6.5)	0.33
Registration of government-certified palliative care workshop, *n* (%)	72 (90%)	117 (77%)	0.02
Psychiatrist on palliative care team, *n* (%)			
Involvement of psychiatric consultation service in palliative care team	80 (100)	110 (73)	<0.001
Full time	19 (24)	11 (7)	
≥50% of protected time	30 (38)	22 (14)	
Hospital, *n* (%)			
Cancer center	8 (10	20 (13)	0.49
University hospital	32 (40)	21 (14)	0.002
Number of inpatients beds	702	590	<0.001
Number of inpatients with cancer in 2007	3723	2573	<0.001
Inpatients with cancer (%) in 2008	30.1	24.7	0.043
Infrastructure of hospital, *n* (%)			
Palliative care units, institution-operated hospice	16 (20)	33 (22)	0.87
Psychiatric ward	44 (55)	54 (35)	0.005
Outpatient clinic	71 (89)	109 (71)	0.003
Consultation-liaison service	76 (95)	134 (88)	0.10
Psychiatrists, median	4	1	<0.001
>5	35 (44)	30 (20)	
2–4	23 (29)	43 (28)	
1	19 (24)	34 (22)	
Palliative care team			
Palliative care physician			
Full-time equivalent positions, median (IQR)	1 (1–3)	1 (0–2)	0.008
Physicians with ≥50% of protected time, median	2	2	0.23
Nurses	1	1	0.83
Pharmacists, median	1	1	0.65

with non-approved palliative care teams. Psychiatric consultation-liaison services and psychiatric outpatient clinics were common in both cancer hospitals with approved palliative care teams and those with non-approved palliative care teams. Only 20% of cancer hospitals offered palliative care units or institution-operated hospices.

Involvement of Psychiatric Consultation-Liaison Services in Palliative Care Programs

Table 2 provides an overview of the involvement of psychiatric consultation-liaison services in palliative care teams. Compared with the cancer hospitals with non-approved palliative care teams, the approved palliative care teams provided twice as many referrals (25 versus 12; $P < 0.001$), conducted rounds with all team members more frequently and held conferences more frequently. Similarly, psychiatrists of approved palliative care teams participated in team rounds and conferences more frequently. On the other hand, only half the consultation-liaison psychiatrists typically attended the rounds of the palliative care teams.

Availability of Psychiatric Services in Palliative Care Programs

Table 3 provides information about the structure and processes of psychiatric consultation-liaison services in palliative care programs. Psychiatric consultation-liaison services

Table 2. Involvement of psychiatric consultation-liaison services in palliative care programs

	Cancer hospitals with approved palliative care teams ($n = 80$)	Cancer hospitals with non-approved palliative care teams ($n = 153$)	*P*-value
Palliative care consultation services			
Availability days per week median (IQR)	5 (3–5)	3 (1–5)	<0.001
Number of referrals (per 2 months)	25	12	<0.001
Frequency of rounds with all team members, *n* (%)			
>1/week	33 (41)	35 (23)	0.001
1/week	42 (53)	88 (59)	
1–3/month	0 (0)	2 (1)	
None	5 (6)	13 (9)	
Frequency of conferences with all team members, *n* (%)			
>1/week	13 (16)	11 (7)	0.008
1/week	60 (75)	109 (73)	
1–3/month	2 (3)	22 (15)	
None	5 (6)	5 (3)	
Contributions to palliative care team, *n* (%)			
Participating in team rounds			
≥80%	42 (53)	62 (41)	0.003
≥40 and <80%	21 (26)	26 (17)	
<40%	17 (21)	64 (42)	
Participating in team conferences			
≥80%	61 (76)	97 (63)	0.02
≥40 and <80%	7 (9)	27 (18)	
<40%	12 (15)	28 (18)	

involved with palliative care teams provided not only inpatient consultations, but also outpatient clinics and family support. Generally, psychiatrists of approved palliative care teams served more patients, followed up more frequently and responded more readily to referrals compared with psychiatrists on non-approved palliative care teams.

Regarding the total time spent for consultations and follow-up, psychiatrists at cancer hospitals with approved palliative care teams committed more of their time to palliative care consultations compared with psychiatrists at cancer hospitals with non-approved palliative care teams. However, the time devoted to palliative care consultations remained at about 12 h/week at cancer hospitals with approved palliative care teams, which had full-time psychiatrists as core members.

Attitudes and Practices of Psychiatrists

Table 4 reveals information about the practice of consultation-liaison psychiatric services involved with palliative care teams provided by consultation-liaison psychiatrists. Table 4 shows the number of hospitals where psychiatric consultation-liaison services adhered to the consultation practices. In both cancer hospitals with approved palliative care teams and those with non-approved palliative care teams, the adherence rates are various by subjects. The adherence rate was high in assessing psychiatric symptoms directly (99% in cancer hospitals with approved palliative care team and 97% in those with non-approved palliative care teams) and assessing prognostic expectations. On the other hands, the adherence rate was low in educating the nursing and support staff regarding aspects of patient management and care planning (29% in cancer hospitals with approved palliative care team and 18% in those with non-approved palliative care teams). The rate of adherence between cancer hospitals with approved palliative care teams and those with non-approved palliative care teams differed in 16 of the 25 measures. For psychiatric assessment, the adherence rate was high (assessing and managing psychiatric symptoms directly, 99 versus 94%). On the other hand, the adherence rate varied for physical assessment (prognostic expectations, pain, activities of daily life), social assessment (financial, family problems, place of care) and coordination (discussing management with the physician directly, educating the staff regarding aspects of patient management).

Table 3. Availability of psychiatric services in palliative care programs

	Cancer hospitals with approved palliative care teams ($n = 80$)	Cancer hospitals with non-approved palliative care teams ($n = 153$)	*P*-value
Psychiatric service provided by palliative care teams, *n* (%)			
Inpatient	80 (100)	153 (100)	>0.99
Outpatient	67 (84)	109 (71)	0.04
Family	57 (71)	88 (58)	0.04
Bereaved family	30 (38)	38 (25)	0.043
Availability (inpatient)			
Response time to a request, *n* (%)			
Within 24 h	60 (75)	77 (51)	<0.001
Within 2–3 days	17 (21)	37 (24)	
Within 1 week	3 (4)	37 (24)	
Responding to an urgent request during business hours	76 (95)	118 (78)	0.001
Responding to an urgent request after office hours, *n* (%)			
Corresponding directly	19 (24)	33 (22)	0.043
By substitution	46 (58)	70 (46)	
Unsupported	15 (19)	47 (31)	
Emergency care			
Corresponding directly	23 (29)	32 (22)	0.31
By substitution	45 (56)	81 (54)	
Unsupported	11 (14)	34 (23)	
Number of referrals/2 weeks, median (IQR)	5.5 (4–10)	4 (2–8)	0.001
Number of rounds for follow-up/week	2 (1–3)	1 (1–2)	<0.001
Days from referral to discharge, median (IQR)	20 (12–30)	20 (7–30)	0.26
1–7 days	12 (17)	36 (27)	
>1–4 weeks	46 (67)	77 (58)	
>1–3 months	10 (15)	17 (13)	
>3 months	1 (1)	1 (1)	
Percentage of patients who died during intervention	30 (10–50)	50 (20–66.25)	0.040
Total time spent on consultation and follow-up (min/week)	741 (555–927)	516 (393–638)	0.002
Availability (outpatient), *n* (%)			
Response time to a request			
Within 24 h	26 (37)	39 (33)	0.45
Within 2–3 days	18 (26)	22 (19)	
Within 1 week	25 (36)	56 (48)	
Responding to an urgent request during business hours	64 (92)	90 (77)	0.016
Responding to an urgent request after office hours			
Corresponding directly	12 (17)	24 (21)	0.85
By substitution	33 (47)	52 (44)	
Unsupported	25 (36)	41 (35)	

DISCUSSION

Our survey provides information on the availability of psychiatric consultation-liaison services involved with palliative care programs in Japanese cancer hospitals. Compared with cancer hospitals with non-approved palliative care teams, those with approved palliative care teams were more likely to integrate psychiatric consultation-liaison services for cancer patients into their palliative care programs. Psychiatrists assessed cancer patients from various

Table 4. Attitudes and practices of psychiatrists

	Cancer hospitals with approved palliative care teams, *n* (%) (*n* = 80)	Cancer hospitals with non-approved palliative care teams, *n* (%) (*n* = 153)	*P*-value
Asking the requesting physician directly how you can best help them			
≥80%	56 (70)	90 (59)	0.07
≥40 and <80	19 (24)	43 (29)	
<40%	5 (6)	20 (13)	
Anticipating potential problems			
≥80%	64 (80)	110 (72)	0.16
≥40 and <80%	13 (16)	31 (20)	
<40%	3 (4)	12 (8)	
Assessing and managing psychiatric symptoms directly			
≥80%	79 (99)	144 (94)	0.10
≥40 and <80%	1 (1)	8 (5)	
<40%	0 (0)	1 (1)	
Reviewing medical records			
≥80%	78 (98)	135 (88)	0.02
≥40 and <80%	1 (1)	15 (10)	
<40%	1 (1)	3 (2)	
Assessing prognostic expectations			
≥80%	74 (93)	124 (81)	0.02
≥40 and <80%	6 (7)	23 (15)	
<40%	0 (0)	6 (4)	
Assessing pain			
≥80%	66 (83)	106 (69)	0.02
≥40 and <80%	10 (13)	25 (16)	
<40%	4 (5)	22 (15)	
Assessing physical symptoms			
≥80%	67 (84)	103 (67)	0.004
≥40 and <80%	9 (11)	21 (14)	
<40%	4 (5)	29 (19)	
Assessing activities of daily life			
≥80%	57 (71)	90 (59)	0.04
≥40 and <80%	14 (18)	30 (20)	
<40%	9 (11)	33 (21)	
Assisting the primary care provider in communicating bad news			
≥80%	71 (89)	129 (85)	0.33
≥40 and <80%	7 (9)	15 (10)	
<40%	2 (2)	9 (5)	
Assessing financial resources			
≥80%	37 (46)	54 (35)	0.01
≥40 and <80%	28 (35)	43 (28)	
<40%	15 (19)	56 (37)	
Referrals to hospice, home care and other placements			
≥80%	47 (59)	63 (41)	0.01
≥40 and <80%	15 (19)	39 (26)	
<40%	18 (23)	51 (33)	

Continued

Table 4. *Continued*

	Cancer hospitals with approved palliative care teams, *n* (%) (*n* = 80)	Cancer hospitals with non-approved palliative care teams, *n* (%) (*n* = 153)	*P*-value
Assessing needs in term of discharge support			
≥80%	42 (53)	59 (39)	0.01
≥40 and <80%	21 (26)	35 (23)	
<40%	17 (21)	59 (39)	
Assessing doctor–patient relationship			
≥80%	48 (60)	78 (51)	0.13
≥40 and <80%	17 (21)	33 (22)	
<40%	15 (19)	42 (27)	
Assessing family problems			
≥80%	56 (70)	85 (56)	0.02
≥40 and <80%	18 (23)	45 (29)	
<40%	6 (7)	23 (15)	
Eliciting the patient's understanding and opinions about the disease and its treatment			
≥80%	65 (81)	106 (69)	0.043
≥40 and <80%	9 (11)	24 (16)	
<40%	6 (8)	23 (15)	
Eliciting the family's understanding and opinions about the disease and its treatment			
≥80%	50 (63)	74 (48)	0.03
≥40 and <80%	20 (25)	47 (31)	
<40%	10 (12)	32 (21)	
Making notations on medical charts			
≥80%	76 (95)	147 (96)	0.68
≥40 and <80%	2 (3)	5 (3)	
<40%	2 (3)	1 (1)	
Planning psychiatric treatment with other team members			
≥80%	64 (80)	109 (72)	0.048
≥40 and <80%	14 (18)	31 (21)	
<40%	2 (3)	11 (7)	
Discussing patient management with the physician directly			
≥80%	58 (73)	81 (53)	0.004
≥40 and <80%	16 (20)	50 (33)	
<40%	6 (7)	22 (14)	
Recommending psychiatric pharmacotherapy			
≥80%	60 (75)	114 (75)	0.85
≥40 and <80%	19 (24)	33 (22)	
<40%	1 (1)	6 (4)	
Implementing medical intervention with permission from the primary team			
≥80%	58 (73)	102 (67)	0.51
≥40 and <80%	7 (9)	22 (15)	
<40%	15 (19)	28 (18)	
Implementing psychotherapeutic intervention with permission from the primary team			
≥80%	67 (84)	109 (72)	0.03
≥40 and <80%	11 (14)	30 (20)	
<40%	2 (3)	13 (9)	

Continued

Table 4. *Continued*

	Cancer hospitals with approved palliative care teams, *n* (%) (*n* = 80)	Cancer hospitals with non-approved palliative care teams, *n* (%) (*n* = 153)	*P*-value
Participating in patient care, with other team members			
≥80%	72 (90)	118 (77)	0.01
≥40 and <80%	8 (10)	29 (19)	
<40%	0 (0)	6 (4)	
Educating the nursing and support staff regarding aspects of patient management and care plan			
≥80%	23 (29)	27 (18)	<0.001
≥40 and <80%	32 (40)	36 (23)	
<40%	25 (31)	89 (59)	
Coordinating a family meeting to discuss further plans for care			
≥80%	23 (29)	39 (26)	0.40
≥40 and <80%	46 (58)	85 (56)	
<40%	11 (14)	28 (18)	

perspectives with physicians, provided direct patient care, educated team members on the mental health domains and had a highly interdisciplinary approach to their work. Although there remains some variability in the infrastructure and delivery of psychosocial care in cancer settings, our results suggest that the integration model as psychiatric consultation-liaison services involved in palliative care teams is gaining acceptance in palliative care settings.

Although many institutions have developed elaborate support programs for a variety of symptoms, psychiatric symptoms and psychological problems of patients with cancer are still unrecognized, resulting in their not being offered access to the needed services (16,19,20,33). The National Comprehensive Cancer Network guidelines recommend screening for distress, which broadly defines emotional disturbances; however, only half the NCCN member institutions in the USA conducted screening to identify distressed patients (34). In palliative care programs, only half the National Cancer Institute cancer centers assessed and managed psychiatric disorders (4). Although various linkage programs, including screening programs and referrals, have been used in attempt to improve the continuity, the optimal system remains uncertain.

The full integration model aims to facilitate deinstitutionalization of dual assessment and pursues the best continuity and coordination for the complex needs (35). The full integration needs specialized types of interventions, expedited access to each other and close collaboration between professionals.

The involvement of psychiatric services in palliative care programs offers an advantage over conventional support programs in the detection and management of psychiatric disorders and psychosocial problems. First, psychiatrists provide medical care together with the palliative care teams, and a formalized mechanism for providing psychiatric services in the usual palliative care programs prevents the failure to connect individuals with the referred providers and gain the patients' acceptance of the referral (22,36,37). Second, psychiatrists assess the mental status and evaluate the decision-making capacity of patients, which contributes to enhanced quality of life for patients and families faced with life-threatening illness. Third, palliative care teams often face difficult settings and conflicting ethical issues. Psychiatrists can recognize and mitigate staff stress and address burnout.

Our survey revealed that cancer hospitals with certified palliative care teams offered integrated services between palliative care and consultation-liaison psychiatry; psychiatrists saw cancer patients with the palliative care teams directly, assessed cancer patients in a comprehensive manner and made the coordination process more effective with other staff members.

Although all of the cancer hospitals reported the provision of psychiatric consultation services, some barriers remain at the level of interaction among different clinicians serving the same patient. In our study, 75% of consultation-liaison psychiatrists on certified palliative care teams were ready to respond to urgent requests (within 24 h). About 30% of consultations were urgent requests (20). Many programs provided inpatient services. However, on an outpatient basis, only 40% of cancer hospitals were prepared for referral to consultation on the same day. Most cancer treatment has shifted from inpatient to ambulatory care settings (38) and the structure and processes must be modified accordingly.

On the other hand, a number of barriers to collaboration remain unresolved. The primary problems with attempts to integrate are structural and financial barriers. The integration requires the palliative care teams to expand their knowledge, perspectives and interest. The integrated palliative care teams have to deal with the needs of various patients appropriately, and it takes time to learn about the capabilities of

the other systems, to decide how to work together and to communicate. They often feel 'consultation fatigue'. Also, the integration requires any of various staff to be involved at the clinical management. The cost of support staff can be overwhelming. For this reason, the approval of palliative care teams for national health insurance coverage encourages and facilitates the provision of psychiatric consultation-liaison services in palliative care programs under today's economic circumstances (25).

Most psychiatrists on palliative care teams see patients for direct consultation, assess their condition from various aspects and educate staff members regarding mental health problems. However, the quality and actual frequency of supportive care at each hospital varies. Psychiatrists are actively engaged in providing psychiatric care as well as coordination among physicians, nursing staff and the palliative care teams. On the other hand, educational activities are low in general. The key component to achieve the goal of full integration is the development of common clinical information systems. In previous studies, integrating information system is effective to facilitate communication between professionals (35). For approved palliative care teams, developing the information systems shared in the teams, such as clinical assessment tools, protocols about psychiatric treatment and education programs are needed. Also, for non-approved palliative care teams, establishment of a close contact and improving links between programs might be realistic strategies, rather than building up the full integration by constraint.

Our study had several limitations. First, the responses from our survey could be biased, because they were based on self-assessment and recalled information. Secondly, the response rate of the cancer hospitals with non-approved palliative care teams was low, possibly because low-activity institutions may be reluctant to participate in this type of survey. This may result in an overestimation of psychiatric consultation-liaison services and palliative care programs in cancer hospitals with non-approved palliative care teams. Third, the gold standard of psychosocial support has not yet been obtained. Although the questionnaire was generated based on a literature review and an expert panel, it has not been validated. The sphere of action of consultation-liaison psychiatry is complex, and it is difficult to identify new measurements for assessing the quality of the programs. It was recently suggested that the patients' subjective well-being and the medical team's difficulty in helping patients might be used to measure the effectiveness of consultation-liaison psychiatry. Further research is needed to improve the measurements applied to the consultation-liaison processes. Fourth, some results of this survey may reflect the impact from differences in country of practice and education.

In conclusion, these results suggest that the integration model between psychiatric consultation-liaison services and palliative care services holds some promise as an acceptable model for improving supportive care for patients with cancer. Although most designated cancer hospitals have a psychiatric consultation-liaison service, significant gaps remain in the delivery of care. Additional research is needed to establish the level of synergistic effect between the psychiatric service and the palliative medicine.

Acknowledgements

We thank the staff who assisted in data management, including Ms. Nobue Taguchi and Ms. Yasuko Uchimura. We are also grateful to all respondents for completing the surveys.

Funding

This study was supported by the Cancer Foundation, Japanese Ministry of Health, Labour and Welfare.

Conflict of interest statement

None declared.

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Psychiatry and Clinical Neurosciences 2011; 65: 77–81 doi:10.1111/j.1440-1819.2010.02170.x

Regular Article

Chronic repetitive transcranial magnetic stimulation increases hippocampal neurogenesis in rats

Eiko Ueyama, MD,[1] Satoshi Ukai, MD, PhD,[1,2]* Asao Ogawa, MD, PhD,[2] Masakiyo Yamamoto, MD, PhD,[2] Shunsuke Kawaguchi, MD, PhD,[2] Ryouhei Ishii, MD, PhD[2] and Kazuhiro Shinosaki, MD, PhD[1]

[1]*Department of Neuropsychiatry, Wakayama Medical University, Wakayama and* [2]*Department of Psychiatry, Osaka University Graduate School of Medicine, Osaka, Japan*

Aim: While the underlying therapeutic mechanisms of repetitive transcranial magnetic stimulation (rTMS) treatment for depression remain unclear, recent animal studies have suggested that hippocampal neurogenesis might be required for the effects of antidepressant treatments including antidepressant drugs and electroconvulsive therapy. The aim of this study was to examine chronic rTMS effects on hippocampal neurogenesis in rats.

Methods: Using a 70-mm figure-of-eight coil, the stimulating parameters were set to 25 Hz and 70% of the rTMS device's maximum power. For 14 consecutive days, bromodeoxyuridine (BrdU) and 1000 pulses of rTMS were administered daily. Cell proliferation in the dentate gyrus was examined with immunohistochemistry.

Results: In the rTMS-treated group, BrdU-positive cells were significantly increased in the dentate gyrus.

Conclusion: Our results suggest that hippocampal neurogenesis might be involved in the antidepressant effects of chronic rTMS.

Key words: depression, hippocampus, neurogenesis, rat, transcranial magnetic stimulation.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) is a technique to repeatedly induce electric currents in a small area of the brain non-invasively. Recently, this technique has been applied to the treatment of several psychiatric and neurological diseases. Many clinical trials of rTMS have been conducted, most of which are for patients with depression.[1,2] Sachdev *et al.* showed antidepressant effects of chronic rTMS in a forced swim test in rodents,[3] and while many studies have examined the neurobiological therapeutic mechanisms of rTMS, they remain unclear.[4,5]

*Correspondence: Satoshi Ukai, MD, PhD, Department of Neuropsychiatry, Wakayama Medical University, 811-1, Kimiidera, Wakayama 641-0012, Japan. Email: ukai@wakayama-med.ac.jp
Received 30 June 2010; revised 3 November 2010; accepted 14 November 2010.

Recent studies have suggested that hippocampal neurogenesis might be required for the effects of antidepressant treatments, although it may not be a major contributor to the development of depression.[6] In mice, antidepressant drug effects were disturbed by X-ray ablation of hippocampal neurogenesis.[7] As well as the chronic administration of several antidepressant drugs, electroconvulsive shock (ECS), analogous to human electroconvulsive therapy, increased hippocampal neurogenesis in rodents[8–10] and non-human primates.[11]

The aforementioned studies suggest that chronic rTMS could increase hippocampal neurogenesis and that this increase might be related to its therapeutic mechanisms on depression. However, to date, only one study has examined the effects of chronic rTMS on hippocampal neurogenesis in rodents and it did not show any significant increase of neurogenesis.[12] The lack of significant effects of rTMS in this study

might be related to non-optimal rTMS conditions, considering that the optimal conditions for rTMS in the treatment of depression in humans and in experimental rodent models are still unknown. Hence, in this preliminary study, we examined chronic rTMS effects on hippocampal neurogenesis in rats using conditions similar to those of Sachdev *et al.*, which showed the antidepressant effects of chronic rTMS in the forced swim test in rats.[3]

METHODS

Animals

Sixteen-week-old male Sprague–Dawley rats (SLC Japan, Shizuoka, Japan) were used for all experiments. Rats were kept under standard conditions with a controlled 12-h light/dark cycle and fed standard diet and tap water *ad libitum*. The experimental protocol was approved by the Committee for Animal Experimentation of Osaka University Medical School. All efforts were made to minimize the number of animals used and their suffering.

rTMS treatment

Rats were randomly assigned to the control group ($n = 5$) or the rTMS-treatment group ($n = 5$). rTMS was administered with a 70-mm figure-of-eight coil using a Magstim Super Rapid (Magstim, Whitland, UK). The rTMS parameters were as follows: stimulating frequency = 25 Hz, stimulating pulse intensity = 70% of the rTMS device's maximum power, train duration = 10 s. Four successive trains of rTMS (1000 pulses per day) were administered daily for 14 consecutive days (14 000 pulses in total). The coil was placed horizontally over the scalp and its handle was aligned parallel with the body of the rat. For sham stimulation of the control group, the coil was placed perpendicular to the scalp and all other conditions were identical to the conditions in the rTMS group. The real and sham rTMS treatments did not induce seizures or any apparent behavioral changes.

Administration of bromodeoxyuridine

Bromodeoxyuridine (BrdU) (40 mg/kg in saline, Sigma, St. Louis, MO, USA), a thymidine analog that labels DNA during the S phase, was intraperitoneally administered to the two groups following the rTMS treatments daily (Fig. 1).

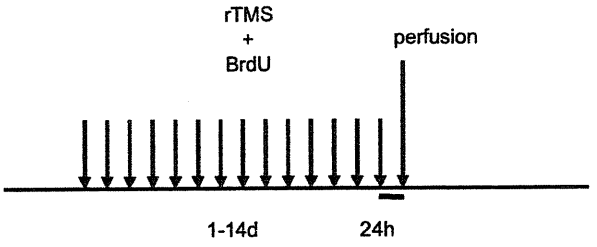

Figure 1. Experimental schema. Repetitive transcranial magnetic stimulation (rTMS) and bromodeoxyuridine (BrdU) were administered daily for 14 consecutive days. Rats were killed 24 h after the last BrdU administration.

Tissue preparation

Twenty-four hours after the last BrdU administration, the rats were deeply anesthetized with sodium pentobarbital and transcardially perfused with saline, followed by 4% paraformaldehyde in 0.1 M phosphate-buffered saline. The brains were removed and postfixed in the same fixative at 4°C overnight and consecutive hippocampal paraffin sections 5 μm thick were prepared.

Immunohistochemistry

After deparaffinizing, slide-mounted sections were incubated in 2 N HCl for 2 h and washed in Tris-buffered saline (TBS). Sections were blocked in TBS containing 10% normal rabbit serum at room temperature (RT) for 1 h and incubated overnight at 4°C with anti-BrdU antibody (1:100, OBT0030, Oxford Biotechnology, Oxford, UK) in TBS containing 10% normal rabbit serum. The next day, the sections were washed and incubated with biotinylated rabbit anti-rat immunoglobulin G (IgG) antibody (1:400, Vector Laboratories, Burlingame, CA, USA) at RT for 1 h. After washing, the sections were incubated with avidin-biotin peroxidase complex (Vectastain Elite ABC Kit, Vector Laboratories) at RT for 1 h. Peroxidase was visualized with 0.05% 3,3′-diaminobenzidine tetrahydrochloride (Sigma) in TBS containing 0.01% hydrogen peroxide. Counterstaining was performed with hematoxylin.

For double immunofluorescence staining, sections were preincubated in TBS containing 5% normal donkey serum and 0.1% Triton X-100 at RT for 1 h, and then incubated with primary antibodies in 3%

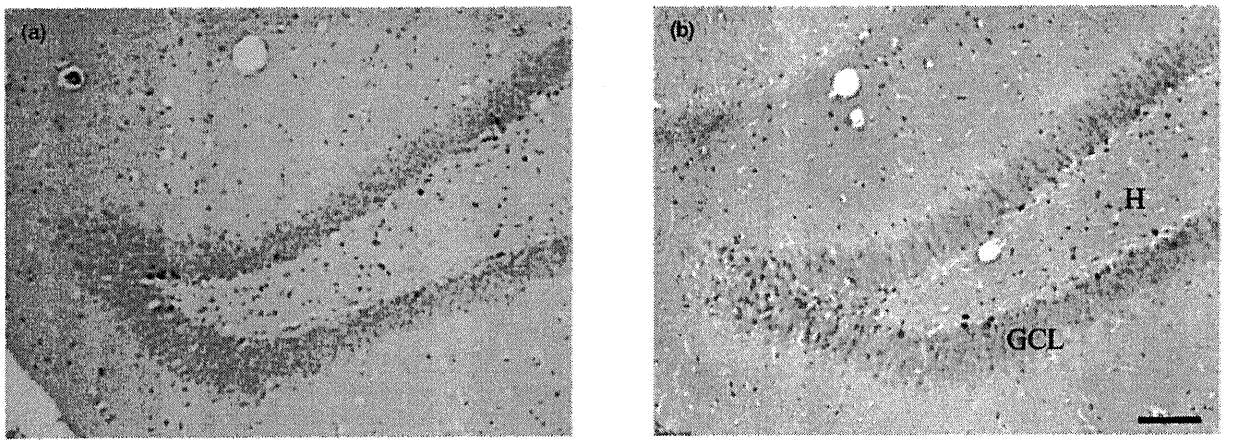

Figure 2. Bromodeoxyuridine-positive cells in the hippocampal dentate gyrus of (a) sham-treated control and (b) repetitive-transcranial-magnetic-stimulation-treated rats. Scale bar: 100 μm. GCL, granule cell layer; H, hilus.

bovine serum albumin (BSA) and 0.1% Triton X-100 overnight at 4°C. The primary antibodies used for immunofluorescence staining were as follows: anti-BrdU, and anti-neuron-specific class III β-tubulin (TuJ1, 1:500, MMS-435P, Covance, Berkeley, CA, USA). After washing, sections were incubated at RT for 1 h with biotinylated donkey anti-rat IgG (1:400, Jackson ImmunoResearch, West Grove, PA, USA) and Cy3-conjugated donkey anti-mouse IgG (1:400, Jackson ImmunoResearch), containing 1% BSA and 0.1% Triton X-100. After rinsing, the sections were incubated with Cy2-conjugated streptavidin (Jackson ImmunoResearch) at RT for 1 h.

Quantitative analysis

Images of immunostained sections were captured from a microscope (Eclipse E800, Nikon, Tokyo, Japan) equipped with a color 3CCD camera (C5810, Hamamatsu Photonics, Hamamatsu, Shizuoka, Japan). The number of BrdU-immunoreactive cells in the granule cell layer (GCL) and the subgranular zone (SGZ, defined as two cell widths below the GCL) of the dentate gyrus was counted in six representative sections (−2.8 mm to −4.5 mm, relative to bregma according to the coordinates of Paxinos and Watson[13]) per animal using Adobe Photoshop software (Adobe Systems, San Jose, CA, USA) in a blinded fashion. The area of the GCL and the SGZ was quantified using NIH Image to estimate the number of BrdU-positive cells per unit area of the dentate gyrus. Statistical analysis was performed on the average number of BrdU-positive cells per section.

For immunofluorescent double labeling, sections were photographed using a Nikon Eclipse E800 microscope equipped with a VFM epi-FL attachment (Kawasaki, Kanagawa, Japan). At least 50 BrdU-positive cells per animal were analyzed to determine the proportions of BrdU-positive cells co-labeling with TuJ1.

The results are expressed as mean ± SEM. Differences between groups were compared using the Student's *t*-test. Statistical significance was defined as $P < 0.05$.

RESULTS

Immunohistochemical staining showed that the majority of BrdU-positive cells were in the SGZ. There were significantly more BrdU-positive cells in the dentate gyrus of the rTMS-treated group as compared with the control group (Figs 2,3). Double immunofluorescence staining showed that most of the BrdU-positive cells were co-labeled with the neuronal marker TuJ1 (Fig. 4). The proportion of cells co-labeled with TuJ1 did not differ significantly between the rTMS-treated and control groups (TuJ1 co-labeled cells, 81.3 ± 2.5% and 80.4 ± 3.1%, respectively).

DISCUSSION

In the present study, we examined the effects of chronic rTMS on neurogenesis in the dentate gyrus of adult rats. Our results showed that the number of

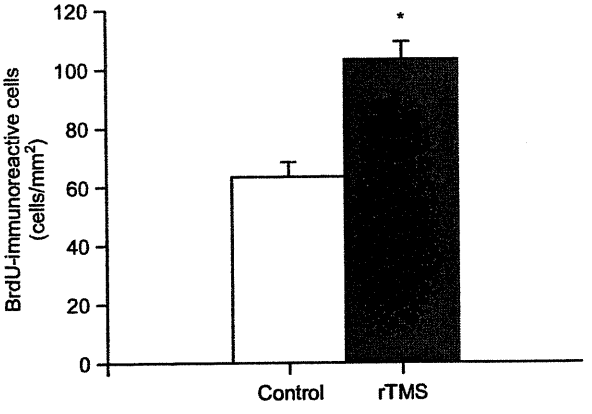

Figure 3. Quantification of bromodeoxyuridine (BrdU)-positive cells in the dentate gyrus. Chronic repetitive transcranial magnetic stimulation (rTMS) treatment significantly increased BrdU-positive cells (Control, 63.1 ± 5.1 cells/mm^2; rTMS, 102.3 ± 6.4 cells/mm^2). Results are shown as mean ± SEM. *$P < 0.05$ vs control.

subgranular progenitor cells was significantly increased in the dentate gyrus. To our knowledge, this is the first report that chronic rTMS increased hippocampal neurogenesis.

Our results are in line with previous studies that showed that chronic treatments with ECS or various antidepressant drugs increase hippocampal neurogenesis in rodents,[6,8–10] and non-human primates.[11] Hence, it appears that hippocampal neurogenesis might be involved in the antidepressant effects of chronic rTMS, although our study did not utilize an animal model of depression or behavioral assessment.

In the present study, we used the similar conditions of chronic rTMS to those described by Sachdev *et al.*, who showed the antidepressant effects of rTMS in the forced swim test.[3] We used the same rTMS device and the same figure-of-eight coil placed over the scalp with identical alignment. The rTMS parameters were also similar to them (25 Hz stimulating frequency, 70% of the rTMS device's maximum power, 1000 pulses per day). The stimulating frequency was set to 25 Hz because Sachdev *et al.* showed that this frequency was most effective among the four frequencies tested (1, 5, 15, and 25 Hz). However, while they assessed the effects of rTMS on the second day after the five daily rTMS treatments, we conducted rTMS treatment for 14 consecutive days according to the schedule of the most recent human clinical trials on depression.[1,2]

Only one study, reported by Czéh *et al.*, has examined chronic rTMS effects on hippocampal neurogenesis in rats, and it showed that neurogenesis was not significantly increased.[12] In contrast with this study, we used a faster stimulating frequency (25 Hz vs 20 Hz) and more total pulses (14 000 pulses vs 5400 pulses). Our use of more powerful chronic rTMS treatment seems to be more appropriate for increasing hippocampal neurogenesis in rats.

The set of the conditions that modulate the intensity and distribution of electric currents and fields

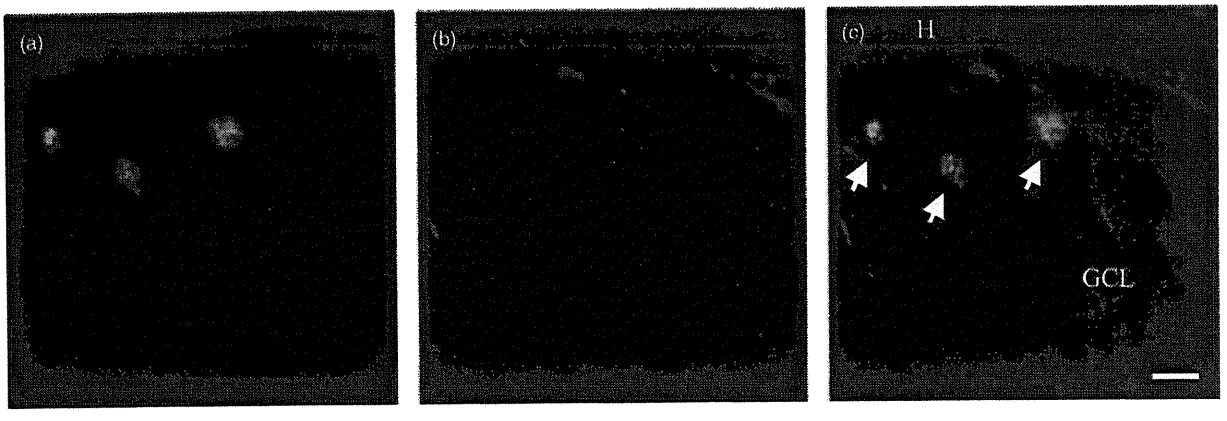

Figure 4. Double labeling with bromodeoxyuridine (BrdU) and neuronal marker anti-neuron-specific class III β-tubulin (TuJ1) after chronic repetitive transcranial magnetic stimulation (rTMS) treatment. Co-localization of (a, green) nuclear BrdU staining and (b, red) cytoplasmic TuJ1 staining. (c) The merged image shows TuJ1-positive cytoplasm surrounding BrdU-labeled nuclei (arrows). Scale bar: 10 μm. GCL, granule cell layer; H, hilus.

induced by a single pulse in the rat brain (e.g. the shape, size, and location of the coil relative to the rodent small brain) is another important consideration.[14] Czéh *et al.* used a smaller round coil over the left frontal brain region and theoretically estimated the characteristics of the intensity and distribution of electric currents and fields.[12] Further studies are needed to evaluate their characteristics in the present study conditions and how they influence the effect of rTMS on hippocampal neurogenesis in rodents.

While most of the previous studies examined hippocampal neurogenesis roughly 1 month after a single or several injections of BrdU, our examinations were conducted on the next day after completion of 14 daily rTMS and BrdU treatments, and we assessed the overall proliferation during the daily treatments. Therefore, our results should be interpreted cautiously when comparisons are made with the results of the previous studies. In addition, the survival of nascent cells was not examined in our study. For more exact comparisons and discussions, further studies will be necessary to set the protocol of the BrdU treatment according to the previous studies under similar conditions of the chronic rTMS of our study.

In conclusion, the present study demonstrated an increase of hippocampal neurogenesis in rats using 14-day chronic rTMS, and it appeared that this increase might be related to the antidepressant effects of rTMS. To examine this relationship more exactly, further studies are needed using an animal model of depression and antidepressant drug-treated animal groups. While a standard rTMS protocol for the treatment of human depression has not been established, our results, even though not directly applicable to humans, could contribute to determining the optimal clinical rTMS conditions for such treatment.

ACKNOWLEDGMENTS

This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of the Japanese Government (13671001) and in part by a grant from Mitsubishi Pharma Research Foundation.

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Psycho-Oncology
Psycho-Oncology (2011)
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.1955

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

Yuki Shirai[1,2], Maiko Fujimori[1,3], Asao Ogawa[1], Yu Yamada[1,2], Yutaka Nishiwaki[4], Atsushi Ohtsu[5] and Yosuke Uchitomi[1,6*]

[1]*Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Japan*
[2]*Research Resident Fellowship from the Foundation for Promotion of Cancer Research Japan for the Third Term Comprehensive 10-Year Strategy for Cancer Control, Japan*
[3]*Okanoya Emotional Information Project, Exploratory Research for Advanced Technology, Japan Science and Technology Agency, Japan*
[4]*Thoracic Oncology Division, National Cancer Center Hospital East, Japan*
[5]*Division of Gastrointestinal Oncology and Digestive Endoscopy, National Cancer Center Hospital East, Japan*
[6]*Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan*

**Correspondence to: Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan. E-mail: uchitomi@md.okayama-u.ac.jp*

Received: 25 May 2010
Revised: 8 February 2011
Accepted: 10 February 2011

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.**

Keywords: cancer; oncology; communication; patient participation; question prompt sheet

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

DOI: 10.1002/pon

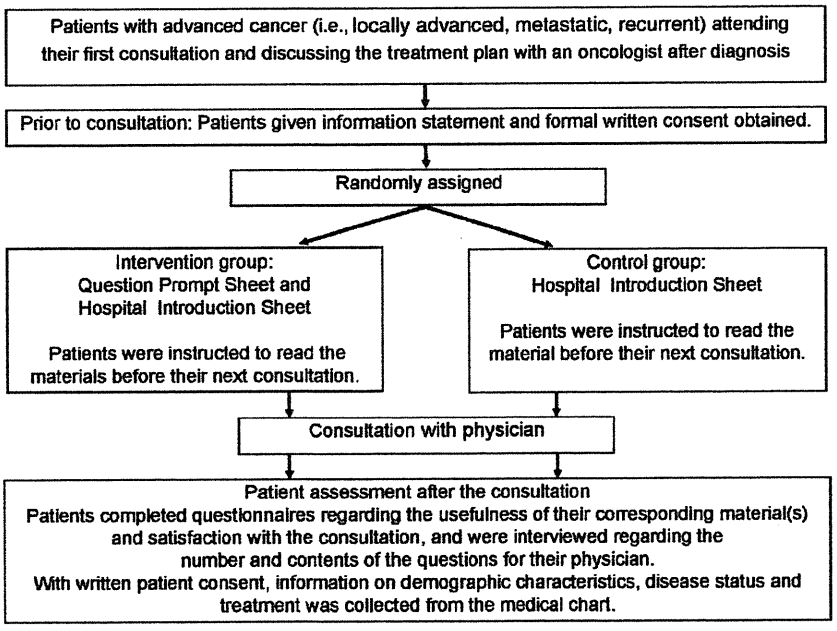

Figure 1. Study procedure

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

DOI: 10.1002/pon

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.

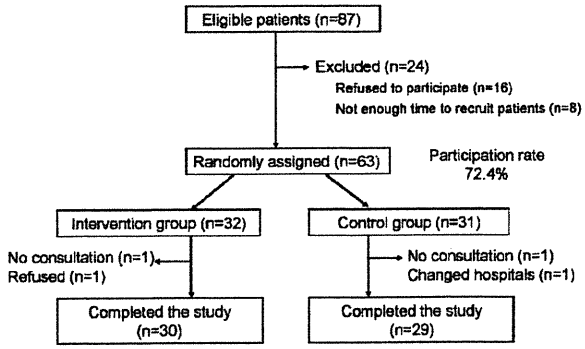

Figure 2. CONSORT diagram

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)

Table I. 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.
[a]Based on intention-to-treat analysis, four drop outs (intervention ($n = 2$); control group ($n = 2$)) were included in the analysis as 'nonuser'.

DOI: 10.1002/pon

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)	p-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)	p-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'.

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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

DOI: 10.1002/pon