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REVIEW ARTICLE

Evaluation of End-of-Life Cancer Care From the Perspective of Bereaved Family Members: The Japanese Experience

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A B S T R A C T

Surveying bereaved family members could enhance the quality of end-of-life cancer care in inpatient palliative care units (PCUs). We systematically reviewed nationwide postbereavement studies of PCUs in Japan and attempts to develop measures for evaluating end-of-life care from the perspective of bereaved family members. The Care Evaluation Scale (CES) for evaluating the structures and processes of care, and the Good Death Inventory (GDI) for evaluating the outcomes of care were considered suitable methods. We applied a shortened version of the CES to three nationwide surveys from 2002 to 2007. We developed the CES as an instrument to measure the structures and processes of care and the GDI as an outcomes measure for end-of-life cancer care from the perspective of bereaved family members. We conducted three nationwide surveys in 1997, 2001, and 2007 (n = 850, 853, and 5,301, respectively). Although six of the 10 areas of the CES showed significant improvements between the two time points investigated, we identified considerable potential for further progress. Feedback from surveys of bereaved family members might help to improve the quality of end-of-life cancer care in inpatient PCUs. However, the effectiveness of feedback procedures remains to be confirmed. Furthermore, there is a need to extend the ongoing evaluation process to home care hospices and general hospitals, including cancer centers, identify the limitations of end-of-life care in all settings, and develop strategies to overcome them.

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INTRODUCTION

It is important to evaluate end-of-life cancer care to determine the quality of care provided by hospices and palliative care units (PCUs). The measurement and the evaluation of end-of-life care play important roles in clinical assessment, research, quality improvement, and public accountability.[1] However, asking the patients themselves for their views on the provision of end-of-life cancer care can be challenging. Many patients are too physically and/or mentally vulnerable to participate in such studies.[2] As a consequence, surveys of terminally ill patients are likely to be unrepresentative and/or biased.[3] As family members are potential proxies for terminally ill patients, it could be useful to conduct surveys of bereaved relatives. To this end, postbereavement evaluations of end-of-life care have been conducted worldwide.

Following pioneering work by Cartwright et al,[4-6] the Regional Study of Care for the Dying was conducted in the United Kingdom in 1990.[7-9] This study involved 3,696 patients, and many secondary findings were reported.[10-13] In the United States, the large-scale Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatments began in 1989.[14] Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatments included a follow-up postbereavement study,[15] and the satisfaction of relatives was measured.[16] Several mortality follow-back surveys have also been conducted in the United States.[17,18] Teno et al[19-22] surveyed patient-centered and family-centered outcomes from a random sample of 1,578 representative individuals who died from chronic illnesses in the United States. Moreover, the National Hospice and Palliative Care Organization surveyed more than 29,292 family hospice users in 2004 and evaluated the care provided using a Web-based approach.[23] The Italian Survey of Dying of Cancer, which evaluated the experiences of Italian patients dying from cancer during 2002 and 2003, was based on a random sample of 2,000 individuals taken from death certificates.[24-26] In addition, numerous surveys have been performed with bereaved family members, including a large-scale survey in the United Kingdom,[27] surveys of intensive care units,[28-31] surveys focusing on the place of care,[32] home care,[33] community hospitals,[34] comparisons

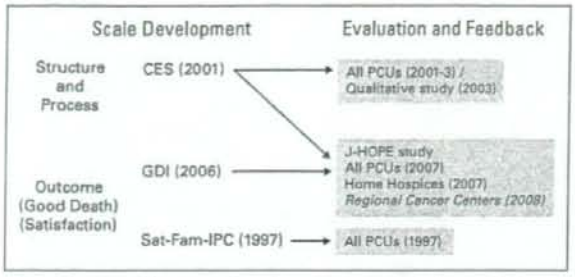

Fig 1. Overview of progress of quality evaluation projects for end-of-life care from the perspective of bereaved family members. CES, Care Evaluation Scale; GDI, Good Death Inventory; PCU, palliative care unit; J-HOPE, Japan Hospice and Palliative Care Evaluation study; Sat-Fam-IPC, Satisfaction Scale for Family Members Receiving Inpatient Palliative Care. Italic text indicates ongoing study.

between hospitals and hospices,[35] and access to hospices,[36] and surveys of end-of-life communication by health professionals,[37] advanced directives and quality of care,[38] and bereavement care.[39]

Obtaining valid measures of bereavement from family members is a crucial problem for many surveys. However, the progress made so far in postbereavement surveys has allowed some instruments to be developed. The Views of Informal Carers Evaluation of Services instrument was developed for the Regional Study of Care for the Dying[40-42] and was subsequently used in the Italian Survey of Dying of Cancer. The Toolkit Instruments to Measure End of life care instrument was developed by Teno et al[43,44] and was used in a subsequent mortality follow-back survey. Curtis et al[45] developed an instrument for assessing the bereaved family members of patients in intensive care units, which is known as the Quality of Dying and Death scale.

In Japan, we have developed measures to evaluate end-of-life cancer care from the perspective of bereaved family members. In addition, we have conducted three nationwide surveys of the quality of hospice and palliative care. An overview of the progress of the quality evaluation of end-of-life care by bereaved family members is shown in Figure 1. A summary of the evaluation studies is presented in Table 1.

The current review describes the progress made in Japanese surveys of bereaved family members and offers some future perspectives.

JAPANESE PALLIATIVE CARE SYSTEM FOR PATIENTS WITH CANCER

The Japanese Ministry of Health, Labor, and Welfare has strongly supported the provision of specialized palliative care services, and PCUs have been covered by National Medical Insurance since 1990. The number of PCUs has dramatically increased from just five in 1990 to 175 in 2007. PCUs for patients with cancer and HIV/AIDS are certified by the prefecture authorities based on several criteria. For example, they must have at least one full-time physician and a sufficient number of nurses, and they must meet structural requirements, such as providing sufficient floor space around beds, a visitor's room, a family room, and so on. Provided that the relevant PCU is certified, the hospital is reimbursed at the rate of 37,800 yen (US$344) per patient per day by the health insurance system. The maximum amount of this fee that the patient pays is 30% or 11,340 yen (US$103).[46] The most common type of specialized palliative care service in Japan is therefore the PCU. However, although the number of PCUs has been increasing, the proportion of deaths covered was only 6% in 2006 (Japanese Ministry of Health, Labor, and Welfare/ Hospice Palliative Care Japan).

The growth of home care hospices has been slow in comparison, and the proportion of home deaths has gradually decreased. In 1960, 64% of deaths resulting from cancer occurred at home, compared with only 6% in 2006 (Japanese census data available online at http://www.mhlw.go.jp). Moreover, although there are several pioneering home care hospices, the numbers of these institutions and of specialized palliative home care practitioners are far lower than in the United States and United Kingdom.[47] Consequently, the Japanese Ministry of Health, Labor, and Welfare defined specialized home care support clinics in 2006. These are expected to provide home care for a wide range of patients in the community, with 24-hour care by physicians or nurses. In addition, these clinics are intended to support

Table 1. Summary of Evaluation Studies in Japan

Year	Instrument	Institutions	No. of Participants	Response Rate (%)	Major Findings
1997	Sat-Fam-IPC	50 PCUs	850	64	Development of Sat-Fam-IPC
					Identification of factors contributing to satisfaction
2001-2003	CES	70 PCUs	853	70	Development of CES
					National level of care evaluation for PCUs by families in 2001-2003
					Triangulation with a qualitative study to explore dissatisfaction with PCUs
					Identification of necessity for improvement of PCUs
2006	GDI	1 regional cancer center	189	57	Development of GDI
					Exploring factors contributing to good death
2007-2008	CES	100 PCUs	5308	69	National level of care evaluation for PCUs, home care hospices, and regional cancer centers by families in 2007-2008
	GDI	14 home care hospices	294	68	*Comparison with 2001-2003 study*
		60 regional cancer centers	*3000-6000 (posting)*	—	*Identification of factors contributing to satisfaction for all care settings*
					Twelve additional questionnaires for PCUs

NOTE. Italics denote ongoing studies.
Abbreviations: Sat-Fam-IPC, Satisfaction Scale for Family Members Receiving Inpatient Palliative Care; PCU, palliative care unit; CES, Care Evaluation Scale; GDI, Good Death Inventory.

community-dwelling patients in cooperation with hospitals, other clinics, PCUs, and visiting nursing services. The clinics can obtain additional remuneration for their work with terminally ill patients at home and for deaths occurring at home. This new home care system is therefore expected to support patients with cancer at home and to increase the proportion of deaths occurring at home. Reports suggest that few of these clinics are involved in a significant number of deaths, suggesting that this system is still early in its development. This system is clearly still in the development phase in Japan.

According to the above-mentioned statistics, more than 80% of patients with cancer died in a general hospital ward. However, the opioid consumption in Japan is one sixth of that in the United States and one seventh of that in the United Kingdom.[48] Despite differences in the legal and medical regulations, as well as cultural differences, these data suggest that pain palliation is not being achieved for patients with cancer in general hospital wards in Japan. As a consequence, in 2002, the Japanese health insurance system established "palliative care additional fee" Palliative Care Team (PCT) services for patients with cancer and HIV/AIDS in general medical wards. This system provides financial support to certified PCTs based on several criteria. For example, the PCT must comprise at least three members of medical staff, including a palliative care physician, a psychiatrist, and a specialized palliative care nurse; at least one physician or nurse must be a full-time staff member who is dedicated to the PCT; and so on. Provided that the relevant PCT is certified, the hospital is reimbursed at a rate of 2,500 yen (US$23) per patient per day by the health insurance system. The maximum proportion of this fee that the patient pays is 30% or 750 yen (US$7).[49] This ground-breaking system is expected to improve the quality of hospital-based palliative care for patients with cancer and their families. However, the number of certified palliative care teams was only approximately 60 in 2007. By contrast, in 2007, there were approximately 8,000 hospitals, including 288 regional cancer centers and 1,113 teaching hospitals in Japan. This system is clearly also in the development stage in Japan.

PROGRESS IN EVALUATION OF END-OF-LIFE CANCER CARE FROM THE PERSPECTIVE OF BEREAVED FAMILY MEMBERS

Step 1. Initial Nationwide Satisfaction Survey for Inpatient PCUs

The Japanese Association of Hospice and Palliative Care Units was established in 1991 to promote the quality of care provided by the certified PCUs belonging to the association. Along with an increase in the number of PCUs, the importance of monitoring the quality of their services has been acknowledged, and a Quality Audit Committee has been established. The committee initially established care standards through panel discussions in 1997. Its next task was to conduct a nationwide survey of bereaved family members to determine their levels of satisfaction with the PCU services.

Before conducting the survey, the Quality Audit Committee developed a postbereavement satisfaction scale instrument. The multidisciplinary committee, which comprised eight palliative care experts, developed the questionnaire through a consensus-building method. The answers to each question were represented on a six-point Likert scale ranging from "very dissatisfied" (0) to "very satisfied"(5). Through a pilot survey, the committee developed a final questionnaire that consisted of 50 questions.[50]

The survey was conducted by mail, and 50 PCUs participated. Of the 1,334 caregivers who were contacted, 850 completed the questionnaires (an effective response rate of 64%). In the development analysis phase, the 50 items were reduced to 34 by a ceiling-effect analysis, principal component analysis, and correlation analysis, which identified redundant items. After a final factor analysis, the resulting Satisfaction Scale for Family Members Receiving Inpatient Palliative Care (Sat-Fam-IPC) was composed of seven subscales: symptom palliation, nursing care, information, facilities, access to an inpatient PCU, family care, and cost. The internal consistency of the Sat-Fam-IPC domains was shown to be satisfactory.[50]

In addition, an explanatory analysis was conducted to clarify the factors contributing to caregiver satisfaction using the Sat-Fam-IPC. This analysis was intended to identify not only the sociodemographic variables but also the organization-related variables that contributed to the Sat-Fam-IPC ratings. The satisfaction score for family care was significantly lower in bereaved individuals who were male, younger, and employed. The satisfaction scores for symptom palliation, facilities, family care, and cost were significantly higher in bereaved relatives of older patients. The satisfaction score for access to an inpatient PCU was significantly lower in cases with shorter admission periods.[50]

Among the organization-related variables, the caregiver satisfaction with nursing care was significantly related to the nursing system, the number of nurses working the night shift, and the presence of attending medical social workers. The satisfaction with symptom palliation was significantly related to the total number of attending physicians and the number of physicians per bed. The satisfaction score for the facilities was significantly higher in the responses from institutions with a larger average floor space per bed. The satisfaction with availability demonstrated a significant positive association with the presence of attending medical social workers. The satisfaction with cost was significantly correlated with the average extra charge for a private room. However, the organization-related variables investigated were not significantly related to the family members' satisfaction with information and family care.[50]

Step 2. Development of the Care Evaluation Scale and Necessity for Improvement of PCUs

Unfortunately, the Sat-Fam-IPC was not well validated and measured the satisfaction only of bereaved family members. In addition, as a general satisfaction scale, the Sat-Fam-IPC showed a skewed distribution in the "satisfied" direction, and a ceiling effect made it difficult to identify the factors that needed to be improved. This type of satisfaction scale also tended to be influenced by the psychological state of the respondent (for example, by depression or grief).[3] Therefore, from 2001 to 2003, we developed the Care Evaluation Scale (CES) as a new instrument to measure the structures and processes of care from the perspective of bereaved family members. The design of the CES was based on pooled data from the following sources: the items used to describe the structures and processes required to assess the quality end-of-life care from the Sat-Fam-IPC, multidisciplinary expert opinion discussions of the Quality Audit Committee, and an extensive systematic literature review. The questions were designed so that the respondents evaluated the necessity to improve each item on a six-point Likert scale ranging from "improvement is not necessary" (1) to "improvement is highly necessary" (6).[51]

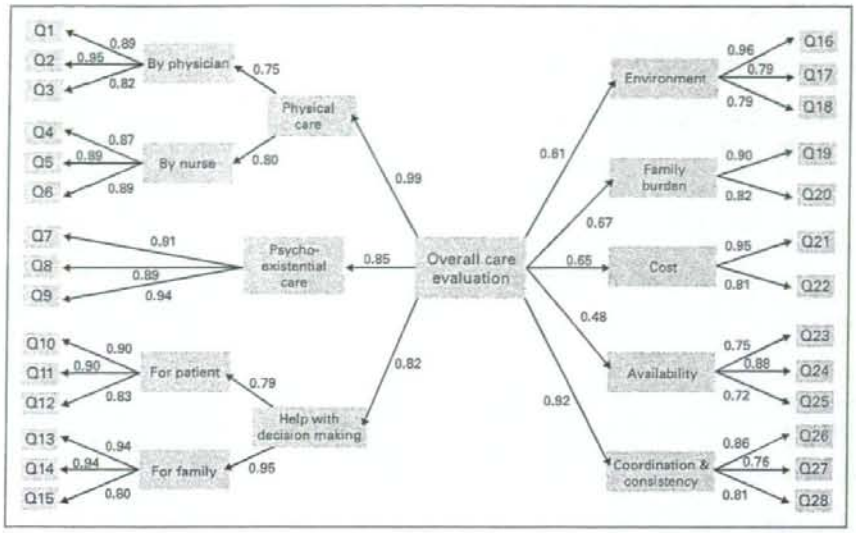

Fig 2. Confirmatory factor analysis of the Care Evaluation Scale.

We then conducted a second nationwide survey of 70 PCUs. The survey was sent in the mail to 1,225 potential participants, 853 of whom responded (an effective response rate of 70%). During the development phase, the respondents were asked to report their perceptions of the necessity for improvement for 67 items. We then reduced the number of items by removing those that had large amounts of missing data, a weak correlation with the overall satisfaction scores, or a skewed distribution. During the validation phase, we conducted two surveys to determine the test-retest reliability. We used a confirmatory factor analysis to examine the construct validity. The final version of the CES comprised 28 items in 10 domains. These domains and examples of the items are shown in Appendix Table A1 (online only). The results of the confirmatory factor analysis are shown in Figure 2. The CES had good psychometric properties (Table 2). In addition, it was not correlated with the depression scale. The CES could thus measure a participant's evaluation of the structures and processes of end-of-life cancer care independent of their psychological condition.[51]

This survey not only evaluated the level of end-of-life care but also identified several areas that needed improvement via a subsequent qualitative interview study. The following areas were highlighted: lack of perceived support for maintaining hope, lack of perceived respect of individuality, perceived poor quality of care, inadequate staffing and equipment, poor availability of timely admission into the PCU, lack of accurate information about PCUs, and economic burden.[52] The results of the survey were fed back to the participating institutions. This feedback process identified the specific weaknesses of each participating PCU, and the institutions were expected to improve these areas in accordance with the findings. This project is thus expected to contribute to the quality control in Japanese PCUs.

Step 3. Development of the Good Death Inventory

Before our third nationwide survey, we developed an outcomes measure for end-of-life cancer care. The CES mainly focused on the structures and processes of end-of-life care. A major goal of palliative

Table 2. Psychometric Properties of CES and GDI

Property	CES	GDI
Reliability		
Alpha	0.87-0.95 (good)	0.74-0.95 (good)
ICC	0.56-0.71 (acceptable)	0.38-0.72 (acceptable)
Validity		
Factor	Sufficient	Sufficient
Construct	Correlated with satisfaction and perceived experience (r = 0.36-0.52 and 0.39-0.60, respectively)	More correlated with overall care satisfaction than CES (total score r = 0.39 and 0.26)
Discriminant	Domains were not correlated with depression, expectation of care, and social desirability	Domains were not correlated with CES items
Sensitivity	Significant differences among clinical settings, such as PCUs, general wards, and hematology wards	Significant differences for some domains between general wards and PCUs

Abbreviations: CES, Care Evaluation Scale; GDI, Good Death Inventory; Alpha, Cronbach's α coefficient; ICC, intra-class correlation coefficient; PCUs, palliative care units.

care is achieving a good dying process.[53-55] However, only a few studies have investigated the concept of a good death as an appropriate outcome of end-of-life cancer care in Japan. We therefore developed a measure for evaluating good death from the perspective of bereaved family members. Initially, we conducted a nationwide qualitative study in Japan to explore the attributes of a good death for 63 participants, including patients with advanced cancer and their families, physicians, and nurses.[56] We then conducted a quantitative study to rate the necessity of a good death among a large sample of the general Japanese population, including bereaved family members.[57]

On the basis of the results of these studies, we developed the Good Death Inventory (GDI) to evaluate whether the patients had a good death from the perspective of bereaved family members. To test this instrument, we surveyed 333 bereaved family members at a regional cancer center in 2006. In total, 189 responses were analyzed (an effective response rate of 57%). The GDI consisted of 30 attributes for core domains and 24 items for optional domains. These domains and examples of the items are shown in Appendix Table A2 (online only). The GDI measured the comprehensive end-of-life care outcomes not only for the structures and processes of care, but also for the physical comfort, relationship, dignity, and psycho-existential domains. The psychometric properties of the GDI were found to be satisfactory (Table 2).[57,58] We therefore confirmed the suitability of these instruments to measure the structures and processes (the CES) and the outcomes (the GDI) of end-of-life cancer care in a postbereavement survey in Japan.

Step 4. Large-Scale Nationwide Evaluation Survey of Inpatient PCUs

In 2007, we began a third large-scale nationwide evaluation survey, known as the Japan Hospice and Palliative Care Evaluation (J-HOPE) study. In total, 100 PCUs participated in the J-HOPE study. We mailed questionnaires to 7,659 participants, and 5,308 responses were analyzed. The questionnaire consisted of a shortened version of the CES (10 items), a shortened version of the GDI (18 items), and some additional questions. Details of the study design and participating institutions are available elsewhere.[59] The results of a comparison of the shortened version of the CES and the 2002 study are provided in Table 3. Among the 10 questions, the following six items showed a statistically significant improvement between 2002 and 2007: the doctors dealt promptly with the discomforting symptoms of the patient (item 1; $P = .0001$); the nurses had adequate knowledge and skills (item 2; $P = .0001$); the staff tried to maintain the patient's hopes (item 5; $P = .0001$); the patient's room was convenient and comfortable (item 6; $P = .0001$); there was good cooperation among staff members, such as doctors and nurses (item 9; $P = .0001$); and consideration was given to the health of the patient's family (item 10; $P = .0001$). However, the following four items did not improve between 2002 and 2007: the doctors sufficiently explained the expected outcome to the patient (item 3; $P = .68$); the doctors sufficiently explained the expected outcome to the family (item 4; $P = .42$); the total cost was reasonable (item 7; $P = .13$); and admission (use) was possible when necessary without waiting (item 8; $P = .98$).

Step 5. Expanding Research to Broader Treatment Settings and Future Perspectives

While implementing the J-HOPE study, we also surveyed Japanese home care hospices using the same questionnaire. In total, 14 home care hospices participated in the study. From the 435 questionnaires that were mailed, 294 responses were received (an effective response rate of 68%). The information obtained from this study was preliminary and only related to home care hospices. We plan to extend the survey to the general wards of regional cancer centers in 2008 and have invited all 288 such institutions in Japan to participate in the study. By March 2008, 70 hospitals had indicated their willingness to participate. Once this survey is completed, we plan to evaluate the end-of-life care provided by the general wards of regional cancer centers and home care hospices and to compare them with the results for the PCUs. Mortality follow-back surveys are difficult to conduct in Japan because of the law for the protection of personal information. It is therefore necessary to approach bereaved relatives in clinical settings. Until now, the main focus of end-of-life care evaluation has been PCUs. However, this research should be expanded to broader treatment settings. It will be important to evaluate not only PCU systems but also specialized home care support clinics, PCTs, the general wards of regional cancer centers, and nursing homes. In addition, the data should be fed back to the institutions as a quality assurance measure. In PCU settings, this data feedback might help to improve the quality of end-of-life cancer care. Such quality control systems should be extended to all hospital or clinical settings for end-of-life cancer care.

ADDITIONAL POSTBEREAVEMENT RESEARCH IN JAPAN

Many surveys of bereaved family members have been conducted in Japan, and their findings have contributed to the development of end-of-life cancer care from both clinical and research viewpoints. The topics of previous research have included the following: the control and treatment of symptoms, such as delirium,[60] appetite loss and bronchial secretion,[61] and sedation;[62,63] psychiatric symptoms, such as a desire for death;[64] decision making, such as late referral to the PCU,[65] and communication about the end point of anticancer treatment;[66] attitudes toward palliative care, such as the notion of a good death and preferences for end-of-life care,[67,68] knowledge about palliative care,[69] and impressions of PCUs;[70] and the experience of home death.[71] As mentioned above, studies of bereaved family members have had an important impact on Japanese end-of-life care settings, not only for the evaluation of end-of-life care but also in solving related problems.

COMMENTS

We conducted systematic nationwide postbereavement studies of PCUs, in the course of which we developed measures of the structures, processes, and outcomes of care. The next task is to expand the evaluation to home care settings, general hospitals, and other clinical settings. A comparison of the CES results between 2002 and 2007 revealed improvements in six of the 10 items tested. This might have been the result of the feedback of data from 2002 to the participating institutions. The satisfaction with the explanations given to patients and family members had not changed because of a ceiling effect: as these items were rated as satisfactory in 2002, no subsequent improvement was perceived. The cost was influenced by the medical and

Table 3. Evaluation of Structures and Processes of Care From 2002 to 2007

Item and Year	Improvement of Structures and Processes of Care: Highly Necessary No.	%	Considerably Necessary No.	%	Necessary No.	%	Slightly Necessary No.	%	Rarely Necessary No.	%	Not Necessary No.	%	*P*
(1) The doctors dealt promptly with discomforting symptoms of the patient													.0001
2002	35	4.1	31	3.6	52	6.1	109	12.8	356	41.7	233	27.3	
2007	63	1.2	127	2.4	325	6.1	606	11.4	2,151	40.5	1,821	34.3	
(2) The nurses had adequate knowledge and skills													.0001
2002	33	3.9	35	4.1	62	7.3	116	13.6	361	42.3	214	25.1	
2007	49	0.9	135	2.5	378	7.1	664	12.5	2,163	40.7	1,703	32.1	
(3) The doctors sufficiently explained the expected outcome to the patient													.6823
2002	15	1.8	33	3.9	56	6.6	128	15.0	263	30.8	194	22.7	
2007	88	1.7	173	3.3	447	8.4	936	17.6	2271	42.8	1,111	20.9	
(4) The doctors sufficiently explained the expected outcome to the family													.4204
2002	33	3.9	30	3.5	38	4.5	94	11.0	293	34.3	322	37.7	
2007	69	1.3	159	3.0	377	7.1	729	13.7	2,149	40.5	1,618	30.5	
(5) The staff tried to maintain the patient's hopes													.0001
2002	29	3.4	27	3.2	41	4.8	86	10.1	329	38.6	271	31.8	
2007	45	0.8	105	2.0	300	5.7	472	8.9	2,096	39.5	2,075	39.1	
(6) The patient's room was convenient and comfortable													.0001
2002	34	4.0	28	3.3	60	7.0	127	14.9	307	36.0	267	31.3	
2007	75	1.4	122	2.3	317	6.0	616	11.6	1,786	33.6	2,192	41.3	
(7) The total cost was reasonable													.1270
2002	27	3.2	21	2.5	76	8.9	96	11.3	346	40.6	236	27.7	
2007	88	1.7	160	3.0	459	8.6	748	14.1	1,871	35.2	1,698	32.0	
(8) Admission (use) was possible when necessary without waiting													.9796
2002	51	6.0	54	6.3	71	8.3	138	16.2	251	29.4	249	29.2	
2007	328	6.2	283	5.3	611	11.5	814	15.3	1,341	25.3	1,719	32.4	
(9) There was good cooperation among staff members, such as doctors and nurses													.0001
2002	27	3.2	32	3.8	50	5.9	96	11.3	343	40.2	266	31.2	
2007	63	1.2	132	2.5	275	5.2	569	10.7	2,209	41.6	1,845	34.8	
(10) Consideration was given to the health of the family													.0001
2002	28	3.3	24	2.8	63	7.4	134	15.7	312	36.6	191	22.4	
2007	61	1.1	143	2.7	378	7.1	756	14.2	2,274	42.8	1,461	27.5	

NOTE. The total numbers of participants were 853 in 2002 and 5,308 in 2007. The sum of the proportions was not 100% due to missing values.

hospital systems and by factors such as the additional fees charged for private rooms. However, the time taken for admission remained a problem.

Another task for future studies is the evaluation of end-of-life care based on patient surveys. To avoid biases in the responses, short and easily administrated measures are needed. The development of quality indicators from reviews of administrative data and/or medical charts could also be helpful to evaluate end-of-life care.[72,73] Such quality indicators will be valuable because their measurement does not burden patients or their families. An important challenge is thus to develop a quality indicator that can easily and accurately be used for the quality control of end-of-life care in Japan.

The evaluation of end-of-life care from the perspective of bereaved family members remains a challenge.[1,2] Many problems persist concerning whether it is appropriate to use proxy raters,[74-77] telephone interviews, or postal questionnaires;[40,78] the timing of the survey;[3,4,42] the sequence of the questions;[79] and the properties of the questionnaire from a cognitive psychology perspective.[80] These issues have not yet been examined in Japan. These methodologic problems must be solved before a comprehensive postbereavement study can be realized.

In summary, we conducted systematic nationwide postbereavement surveys of PCUs in Japan and developed measures to evaluate end-of-life care from the perspective of bereaved family members. The care evaluation by family members improved between 2002 and 2007. Feedback from such surveys could help to improve the quality of end-of-life cancer care in PCUs; however, the effectiveness of feedback procedures remains to be confirmed. Future studies should expand the ongoing evaluations to home care settings, general hospitals, and other clinical settings to identify and overcome current limitations. There is also a need to develop measures for patients with advanced

cancer and to identify quality indicators from reviews of administrative data and/or medical charts.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Psychotherapy for depression among incurable cancer patients (Review)

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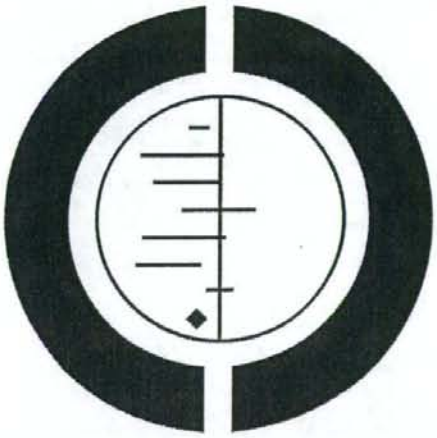

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ABSTRACT

Background
The most common psychiatric diagnosis among cancer patients is depression; this diagnosis is even more common among patients with advanced cancer. Psychotherapy is a patient-preferred and promising strategy for treating depression among cancer patients. Several systematic reviews have investigated the effectiveness of psychological treatment for depression among cancer patients. However, the findings are conflicting, and no review has focused on depression among patients with incurable cancer.

Objectives
To investigate the effects of psychotherapy for treating depression among patients with advanced cancer by conducting a systematic review of randomized controlled trials (RCTs).

Search strategy
We searched the Cochrane Pain, Palliative and Supportive Care Group Register, The Cochrane Controlled Trials Register, MEDLINE, EMBASE, CINAHL, and PsycINFO databases in September 2005.

Selection criteria
All relevant RCTs comparing any kind of psychotherapy with conventional treatment for adult patients with advanced cancer were eligible for inclusion. Two independent review authors identified relevant studies.

Data collection and analysis
Two review authors independently extracted data from the original reports using standardized data extraction forms. Two independent review authors also assessed the methodological quality of the selected studies according to the recommendations of a previous systematic review of psychological therapies for cancer patients that utilized ten internal validity indicators. The primary outcome was the standardized mean difference (SMD) of change between the baseline and immediate post-treatment scores.

Main results
We identified a total of ten RCTs (total of 780 participants); data from six studies were used for meta-analyses (292 patients in the psychotherapy arm and 225 patients in the control arm). Among these six studies, four studies used supportive psychotherapy, one adopted cognitive behavioural therapy, and one adopted problem-solving therapy. When compared with treatment as usual, psychotherapy was associated with a significant decrease in depression score (SMD = -0.44, 95% confidence interval [CI] = -0.08 to -0.80). None of the studies focused on patients with clinically diagnosed depression.

Authors' conclusions
Evidence from RCTs of moderate quality suggest that psychotherapy is useful for treating depressive states in advanced cancer patients. However, no evidence supports the effectiveness of psychotherapy for patients with clinically diagnosed depression.

PLAIN LANGUAGE SUMMARY

Psychotherapy for depression among cancer patients who are incurable

Depressive states represent frequent complications among cancer patients and are more common amongst advanced cancer patients. Psychotherapy comprises of various interventions for ameliorating or preventing psychological distress conducted by direct verbal or interactive communication, or both, and is delivered by health care professionals. It is a patient-preferred and promising strategy for treating depressive states among cancer patients. Several systematic reviews have investigated the effectiveness of psychotherapy for treating depressive states among cancer patients. However, the findings are conflicting, and no review has focused on depressive states among patients with incurable cancer. The review authors conducted a systematic review of randomised controlled trials to investigate the effects of psychotherapy on the treatment of depressive states among patients with advanced cancer. The review authors found that psychotherapy was useful for treating depressive states in advanced cancer patients. However, little evidence supports the effectiveness of psychotherapy for patients with clinically diagnosed depression including major depressive disorder. Future studies to investigate and clarify the usefulness of psychotherapy for treating clinically diagnosed depression in terminally ill patients are needed.

BACKGROUND

Cancer is a life-threatening disease that often impacts on a patient's welfare and well-being; attention to these issues is thus an important aspect of comprehensive patient care. Derogatis *et al.* found that 50% of cancer patients are diagnosed with a psychiatric disorder. The most common psychiatric diagnosis was depressive disorders, including adjustment disorder with depressed mood (12%) or mixed emotional features (13%) or unipolar major depression, (4%) or both (Derogatis 1983). Other studies have consistently indicated that these depressive disorders represent common forms of psychological distress experienced by cancer patients (Akechi 2001; Kugaya 2000; Okamura 2000) and are more common in patients with advanced cancer (Bukberg 1984; Kugaya 2000). Thus depression is one of the most widely recognized psychiatric disorders in cancer patients (McDaniel 1995). Depression not only produces serious suffering (Block 2000), but also worsens quality of life (Grassi 1996), reduces compliance with anti-cancer treatment (Colleoni 2000), can lead to suicide (Henriksson 1995), is a psychological burden on the family (Cassileth 1985), and prolongs hospitalization (Prieto 2002). Thus, the appropriate management of depression in cancer patients is critically important.

One patient-preferred and promising strategy for treating depression among cancer patients is psychotherapy (Okuyama 2007). Here, the term 'psychotherapy' is defined as various kinds of interventions for ameliorating or preventing psychological distress conducted by direct verbal or interactive communication, or both, delivered by health care professionals. Several meta-analyses and systematic reviews investigating the effectiveness of psychosocial treatment for depression among cancer patients have been performed. However, the findings of these reports are conflicting (Devine 1995; Newell 2002; Ross 2002; Sheard 1999), and no review to date has addressed the effectiveness of psychotherapy for treating depression among incurable cancer patients.

OBJECTIVES

1) The primary objective of this review was to investigate the effectiveness of psychotherapy for treating any kind of depression in incurable cancer patients.
2) The review also evaluated the effectiveness of psychotherapy on:

- anxiety,
- general psychological distress,
- control of cancer symptoms,
- quality of life,
- coping measures for patients,
- severity of physical symptoms such as pain.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All relevant randomised controlled trials (RCTs) comparing any kind of psychotherapy with conventional treatment (treatment as usual).

Types of participants

The study participants were limited to adults (18 years or older) of either sex with any primary diagnosis of incurable cancer. Their depression had to be assessed by validated measures, such as standardized self-report questionnaires or clinical interviews (e.g., Structured Clinical Interview for major depressive episode based on DSM-IV). A concurrent diagnosis of another physical disease was not a criteria for exclusion.

Types of intervention

Studies involving psychotherapy of any kind were included in the review. We were interested in the effect of a broad range of psychological interventions, including several unique interventions, such as music therapy, that may be used in a palliative care setting. On the other hand, interventions that were not considered as forms of psychotherapy (e.g., aromatherapy, therapeutic touch) were not included. This broad range of non-pharmacological interventions were further divided into:
A: interventions by direct verbal or interactive communication, or both, delivered by health care professionals; and
B: non-pharmacological interventions other than the aforementioned ones.

Types of outcome measures

The studies had to include at least one measure of the severity of depression, which was set as the primary outcome of this systematic review. Symptom severity could be measured either by self-reporting or rating by an observer.

Effectiveness was to be evaluated using the group mean scores of these continuous depression severity scales (this planned analytical method was modified in the completed review (*See* 'Results')).

Outcomes were to be measured at the end of the study. Where possible, these indices of effectiveness would be pooled at different time points in the course of treatment, such as at one month, three months, six months and so on. In addition, when studies provided data regarding ongoing effectiveness after treatment termination, this data was also to be pooled (this planned method was modified (*See* 'data synthesis').

Secondary outcomes were as follows:
1) no of patients who 'responded' to treatment according to the original study authors' definition;
2) anxiety, as measured using scales like the Hamilton Anxiety Rating scale, the State-Trait Anxiety Inventory, and the Hospital Anxiety and Depression Scale;
3) general psychological distress, as measured using scales like the Profile of Mood States (total mood disturbance) and the General Health Questionnaire;
4) quality of life, as measured using scales like the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire, the Functional Assessment of Cancer Therapy-General (FACT-G) scale, and the Medical Outcome Study Short-Form 36-item survey;
5) severity of physical symptoms like pain, as measured using scales like the Brief Pain Inventory (BPI) and visual analogue scale (VAS).

Tolerability of the treatment was to be evaluated using the following outcome measures:
1) Number of patients dropping out of the study for any reason.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Pain, Palliative and Supportive Care Group methods used in reviews.

1. Electronic databases

To identify studies for inclusion in this review, detailed search strategies were developed for each electronic database searched in September 2005. These strategies were based on the search strategy developed for MEDLINE but were revised appropriately for each database and are included in additional Table 01.

MEDLINE via OVID search strategy
1. exp PSYCHOTHERAPY/
2. (psychotherap$ or aromatherap$ or "art therap$" or "autogenic training" or "behavior$ adj6 therap$" or (behaviour$ adj6 therap$) or (biofeedback and psycho$) or (cognitive adj6 therap$) or (desensiti$ and psychol$) or "implosive therap$" or (relax$ adj6 therap$) or (relax$ adj6 techniq$) or (therap$ adj6 touch$) or yoga)
3. (bibliotherapy or (color$ adj6 therap$) or (colour$ adj6 therap$) or (music$ adj6 therap$) or (hypno$ adj6 therap$) or (imagery and psychotherap$) or counsel$ or (group$ adj6 therap$) or "socioenvironmental therap$" or "socio environmental therap$" or "milieu therap$" or "therapeutic communit$" or (famil$ adj6 therap$) or psychosoc$ or psycholog$ or "self help group$" or (support$ adj6 group$) or (guide$ adj6 image$))
4. or/1-3
5. Depression/
6. (depression or depressive$ or depressed)
7. or/5-6
8. exp NEOPLASMS/
9. (tumor$ or tumour$ or cancer$ or carcinoma$ or malignan$ or neoplas$)
10. or/8-9
11. 4 and 7 and 10

The above search strategy was run with the following filter for Controlled Clinical Trials:
Cochrane Sensitive Search strategy for RCTs for MEDLINE on OVID (published in appendix 5b Cochrane Handbook for Systematic Reviews of Interventions. 4.2.5 May 2005)
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized controlled trials.sh.
4. random allocation.sh.
5. double blind method.sh.
6. single blind method.sh.
7. or/1-6
8. (ANIMALS not HUMAN).sh.
9. 7 not 8
10. clinical trial.pt.

11. exp clinical trials/
12. (clin$ adj25 trial$).ti,ab.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
14. placebos.sh.
15. placebo$.ti,ab.
16. random$.ti,ab.
17. research design.sh.
18. or/10-17
19. 18 not 8
20. 19 not 9
21. 9 or 19

2. Reference search
The references of all selected studies were inspected for more published reports and citations of unpublished studies. In addition, other relevant review papers were checked.

3. SciSearch
All the selected studies were sought as a citation in the SciSearch database to identify additional studies.

4. Personal communication
To ensure that all RCTs were identified, the authors of significant papers were contacted.

5. Language
No language restrictions were applied when selecting studies.

METHODS OF THE REVIEW

1. Selection of studies
In September 2005, two review authors (TA and JO) checked hard copies of the references identified by the search strategy to identify studies meeting the following broad and simple criteria:
i) randomised trials;
ii) incurable cancer patients (this included subjects with incurable, advanced, metastatic, or terminal cancer. When the participants were mixed-stage cancer patients, studies in which more than 80% of the participants had an advanced stage of cancer (stage III, IV, or recurrent) were eligible for inclusion in the review); and
iii) assessment of depression.

The inter-rater reliability of the two raters were evaluated using percentage agreement and kappa coefficient. All studies identified by either of the two raters were then subjected to the next stage of critical appraisal according to the strict eligibility criteria.

2. Quality assessment
Two independent review authors (TA and TO) assessed the methodological quality of the selected studies. We used Newell's methodological quality criteria (Newell 2002), which includes the following points:
i) adequate concealment of allocation;
ii) patients randomly selected;
iii) patients blinded to treatment group;
iv) care-providers blinded to treatment group;
v) except for study intervention, equivalence of other treatments;
vi) care-providers' adherence monitored;
vii) detailed lost-to-follow-up information;
viii) percentage of patients not included in analyses;
ix) intention-to-treat analyses; and
x) outcomes measured in a blinding fashion.

The maximum score for each study was 30 points, with higher scores indicating higher quality. As previously reported, the quality of a study was considered to be good if the study had a total score greater than 20 points, fair if it scored 11 to 20 points, and poor if it scored less than 11 points (Newell 2002).

The inter-rater reliability of these validity criteria was evaluated using Cohen's weighted kappa. Those studies with clearly inadequate concealment of random allocation were excluded. The influences of the other quality indices were examined using sensitivity analyses.

3. Data extraction
Two review authors (TA and TO) independently extracted data from the original reports using data extraction forms. Any disagreement was resolved by consensus between the two or, where necessary, between all the review authors. Extracted data included the country of origin, the nature and content of psychological intervention and the patient group involved, the duration of the study, the study setting, the sample size, and the key outcomes using validated instruments.

4. Data synthesis
Planned method
Data were to be entered by JO into Review Manager 4.2.10 twice, using the duplicate data entry feature. For dichotomous outcomes, the relative risk (RR) and their 95% confidence intervals (CI) were to be calculated using the random-effects model, since the RR of the random-effects model has been shown to be superior in clinical interpretability and external generalisability than the fixed-effect models and odds ratios (OR) or risk differences (Furukawa 2002). The heterogeneity among the studies was to be assessed using the I-squared and Q statistics and by visual inspection of the results in the Meta View plots. An I^2 greater than 30% or a Q statistic P value of less than 0.1 was to be considered indicative of heterogeneity. If significant heterogeneity was suspected, the sources were to be investigated. For dichotomous outcomes of response, two analytical strategies were to be adopted; first, a 'per protocol' analysis was to be performed according to the values reported by the original authors. When data on dropouts were included, usually by way of the last-observation-carried-forward (LOCF) method, this data was to be analysed according to the primary studies. For continuous outcomes, the standardized mean difference (SMD) was to be pooled using the random-effects model. Continuous outcomes were to be analysed on an endpoint basis, including only patients with a final assessment or with a last

observation carried forward to the final assessment. A strict ITT analysis was not feasible with continuous outcomes, as the studies performed only LOCF or endpoint analyses.

Actual method

Data were entered by TA into Review Manager 4.2.10 twice using the duplicate data entry feature. Analysis of dichotomous outcomes was planned, but only one study (Wu 2003) included this. Post-treatment scores were available in three studies (Wu 2003; Liossi 2001; Linn 1982) while change scores were available or could be calculated in six studies (Goodwin 2001; Classen 2001; Edelman 1999; Wood 1997; Linn 1982; Spiegel 1981). We therefore modified the data synthesis method during the review because the data obtained could not be synthesized appropriately using the planned method. The change between the baseline and immediate post-treatment scores was selected as the primary outcome for the meta-analysis (Banerjee 2006). The SMD and 95% CIs were pooled using a random-effects model (Alderson 2004). Two studies provided data on the results of slope analyses (Classen 2001; Spiegel 1981), and we calculated the change scores using these data. One paper provided raw data only (Wood 1997); for these data, we calculated the change score using SPSS 10.0J version software for Windows (SPSS 2003). In addition, because we could not obtain the actual figures for the standard deviations in the change scores for depression, anxiety, and general psychological distress in two studies (Classen 2001; Linn 1982), we calculated the pooled standard deviations in the other available studies that utilized the same measuring instrument (the Profile of Mood States) (MaNair 1992) (Edelman 1999; Goodwin 2001; Spiegel 1981; Wood 1997) and these values were inputted for the missing data (Furukawa 2006).

The heterogeneity among the studies was assessed using the I^2 and Q statistics and by visual inspection of the results in Meta View plots. An I^2 value greater than 30% or a Q statistic with a P value less than 0.1 were considered indicative of heterogeneity. If significant heterogeneity was suspected, the source of it was investigated.

5. Subgroup analyses

Subgroup analyses should be performed and interpreted with caution because multiple analyses can lead to false-positive conclusions (Oxman 1992). However, we performed the following subgroup analyses, if possible, for the following *a priori* reasons:

- A separate analysis was performed for participants who received group psychotherapy, since different modalities of psychotherapy (i.e., group versus individual) could have different effects.
- A separate analysis was performed for breast cancer patients, because many psycho-oncology studies focus on this patient group.
- A separate analysis was performed for participants with clinical depression based on any cut-off points or diagnostic criteria of depression measures, because the effect of psychotherapy on depression may differ according to the baseline depressive status.
- A separate analysis was performed for participants receiving interventions by direct verbal or interactive communication delivered by health care professionals, or both, because this type of psychotherapy may have a different effect on depression.

6. Funnel plot analysis and sensitivity analyses:

- A funnel plot analysis was performed to check for any publication bias.
- A sensitivity analysis was performed, if possible, to examine the robustness of the observed findings by repeating all the analyses using only high-quality studies.

DESCRIPTION OF STUDIES

Two independent review authors checked the studies identified by the search sources, and a total of 176 studies were extracted for possible inclusion. Full copies of these articles were obtained, and the two independent review authors then examined the strict eligibility of these papers. Further reference searches and a SciSearch did not yield any additional studies that satisfied the strict eligibility criteria. The inter-rater reliability of the strict eligibility criteria were as follows: kappa coefficient, 0.84, percent concordance, 95.5%.

First, we identified 16 studies that were potentially suitable for inclusion (Classen 2001; Edelman 1999; Giasson 1998; Goodwin 2001; Laidlaw 2005; Linn 1982; Liossi 2001; Mantovani 1996; North 1992; Sarna 1998; Schofield 2003; Sloman 2002; Soden 2004; Spiegel 1981; Wood 1997; Wu 2003). However, five of these studies (Giasson 1998; North 1992; Sarna 1998; Schofield 2003; Soden 2004) were ultimately dropped after a discussion among the review authors because the interventions in these studies were not forms of psychotherapy. The interventions in these studies were as follows: aromatherapy (Soden 2004), a multisensory environment (Schofield 2003), a structured nursing assessment of symptoms (Sarna 1998), noncontact therapeutic touch (Giasson 1998), and information provided by tape-recordings of consultations (North 1992). In addition, one study was excluded because of the absence of usual care in the control group (Mantovani 1996). Finally we identified ten studies that were suitable for inclusion (total of 780 participants) (Classen 2001; Edelman 1999; Goodwin 2001; Laidlaw 2005; Linn 1982; Liossi 2001; Sloman 2002; Spiegel 1981; Wood 1997; Wu 2003).

The subjects of the meta-analysis were recruited from three main groups: patients with metastatic breast cancer (five studies), patients who had received some form of palliative care (three studies), and various patients with advanced cancer (two studies).

Various types of interventions were utilized in these ten studies. Five studies (Classen 2001; Goodwin 2001; Linn 1982; Spiegel

1981; Wu 2003) mainly used supportive psychotherapy. Three studies mainly investigated the effect of behavioural therapies, either relaxation techniques (Sloman 2002) or hypnosis (Laidlaw 2005; Liossi 2001). The other studies used cognitive behavioural therapy (Edelman 1999) and problem-solving therapy (Wood 1997). The duration of the interventions was variable, ranging from just three to five sessions (Wood 1997) to unlimited and continuing until death (Spiegel 1981). Three of the five studies using supportive psychotherapy and the one study using cognitive behavioural therapy utilized group treatment sessions. Thus, the ten selected studies included several kinds of interventions, all of which involved direct verbal and interactive communication delivered by health care professionals (Classen 2001; Edelman 1999; Goodwin 2001; Laidlaw 2005; Liossi 2001; Linn 1982; Sloman 2002; Spiegel 1981; Wood 1997; Wu 2003). There were no interventions belonging to non-pharmacological interventions other than the aforementioned ones.

METHODOLOGICAL QUALITY

With regard to study quality, none of the studies met the criteria for a 'good' rating. Three studies met the criteria for a 'fair' rating (Goodwin 2001; Linn 1982; Wu 2003), and the remaining seven studies were judged as having a 'poor' rating. Two studies clearly described the procedure for adequate allocation concealment (Goodwin 2001; Linn 1982).

RESULTS

Two studies did not report the effects of the interventions on depression (Laidlaw 2005; Wood 1997), although they did measure the severity of depression among the participating subjects. As described above, all of the remaining eight studies used interventions involving direct verbal and interactive communication delivered by health care professionals (Classen 2001; Edelman 1999; Goodwin 2001; Linn 1982; Liossi 2001; Sloman 2002; Spiegel 1981; Wu 2003).

Effects of psychotherapy on depression: meta-analyses

Moderate and statistically significant heterogeneity among six studies (see below) was observed (P = 0.004, I^2 = 71%). The identified studies were quite heterogeneous with regard to their participants and interventions, and many studies did not include some of the data required for meta-analyses. Consequently, we decided to conduct the meta-analyses by combining the data from studies in which the change scores were available. Thus, we excluded four studies because they did not contain necessary data, such as the change score, the standard deviation of the change score, or the number of participants (Laidlaw 2005; Liossi 2001; Sloman 2002; Wu 2003). The data from the six studies that provided all the information needed to conduct the meta-analyses were combined; all of these studies had used the Profile of Mood States as a measure of depression (Classen 2001; Edelman 1999; Goodwin 2001; Linn 1982; Spiegel 1981; Wood 1997). Among these six studies, four studies used supportive psychotherapy (Classen 2001; Goodwin 2001; Linn 1982; Spiegel 1981), one utilized cognitive behavioural therapy (Edelman 1999) and one utilized problem-solving therapy (Wood 1997). Regarding the data from the study by Linn *et al.*, we decided to use the data obtained one month after intervention to minimize the effects of drop-outs, although the study provided data on depression at five time points during the intervention (Linn 1982).

The combined data from the six studies, involving 292 patients in the psychotherapy arm and 225 patients in the control arm, showed that psychotherapy had a significant effect on the treatment of depression among participants with advanced cancer (SMD = -0.44, 95% CI = -0.08 to -0.80). Visual inspection of the Meta View plots suggested that the study conducted by either Spiegel *et al.* or Wood *et al.* contributed most of the heterogeneity (Wood 1997; Spiegel 1981). While the heterogeneity indicators were similar if the study by Wood *et al* (Wood 1997) was excluded (Chi^2 = 15.49, df = 4 (P = 0.004), I^2 = 74%), the heterogeneity diminished and was no longer statistically significant if the study by Spiegel *et al* was excluded (Chi^2 = 5.93, df = 4 [P = 0.20], I^2 = 32.6%). The source of the heterogeneity was further investigated by examining the patient group, measuring instrument, type and duration of intervention, treatment of control group, outcome data and so on; however, clear factors that might have produced the heterogeneity could not be identified.

Effect of psychotherapy on anxiety and general psychological distress: meta-analyses

Since one study did not measure anxiety (Linn 1982), we combined the data from five studies (Classen 2001; Edelman 1999; Goodwin 2001; Spiegel 1981; Wood 1997). The combined data, involving 242 patients in the psychotherapy arm and 169 patients in the control arm, showed that psychotherapy had a borderline effect on anxiety among participants with advanced cancer (SMD = -0.68, 95% CI = 0.01 to -1.37). Strong, statistically significant heterogeneity was observed (P < 0.00001, I^2 = 89.1%). Visual inspection of the Meta View plots suggested that the study conducted by Spiegel *et al.* was heterogeneous (Spiegel 1981). When this study was omitted, the significant heterogeneity was no longer observed (Chi^2 = 3.22, df = 3 [P = 0.36], I^2 = 6.8%).

Four studies provided data on general psychological distress, as evaluated using the total mood disturbance score of the POMS (Classen 2001; Edelman 1999; Goodwin 2001; Spiegel 1981). The combined data, involving 237 participants in the psychotherapy arm and 166 participants in the control arm, showed a significant effect for psychotherapy on general psychological distress among participants with advanced cancer (SMD = -0.94, 95% CI = -0.01 to -1.87). A strong, statistically significant heterogeneity was observed (P < 0.00001, I^2 = 94.3%). Visual inspection of the Meta View plots again suggested that the study conducted by

Spiegel *et al.* was heterogeneous (Spiegel 1981). When this study was omitted, the significant heterogeneity was no longer observed ($Chi^2 = 2.43$, df = 2 (P = 0.30), $I^2 = 17.8\%$).

Other secondary outcomes

We deleted some secondary endpoints, including symptom control, quality of life, coping measures for participants, and severity of physical symptoms (like pain), because few studies provided this kind of data. In addition, we stopped checking the tolerability of the treatment and the dichotomous outcomes for the same reason.

Subgroup and sensitivity analyses

The two planned subgroup analyses (for participants who underwent group psychotherapy and for breast cancer patients) were conducted using the same four studies that investigated the effectiveness of group psychotherapy among metastatic breast cancer patients (Classen 2001; Edelman 1999; Goodwin 2001; Spiegel 1981). The results demonstrated similar and significant findings for all three targeted psychological symptoms: depression, anxiety, and general psychological distress.

The other subgroup analysis (for participants with clinical depression) was not conducted as none of the studies included the participants with clinically diagnosed depression. In addition, as described in the aforementioned section ('Effects of psychotherapy on depression: meta-analyses'), the planned subgroup analysis for participants receiving interventions via direct verbal and interactive communication delivered by health care professionals was not performed.

As only two studies included in the meta-analysis were judged to be of good or fair quality (Goodwin 2001; Linn 1982), a sensitivity analysis limited to these studies was performed. However, the study conducted by Linn *et al.* did not include anxiety and general psychological distress measures, so we conducted the sensitivity analysis for depression only. The combined data, involving 152 patients in the psychotherapy arm and 101 patients in the control arm, showed that psychotherapy was significantly effective for the treatment of depression (SMD = -0.35, 95% CI = -0.06 to -0.65). Statistically significant heterogeneity was not observed (P = 0.26, $I^2 = 22.4\%$).

Although the number of included studies was small, thereby limiting the usefulness of a visual inspection of the funnel plot (Figure 01; Figure 02; Figure 03), a visual inspection did not suggest a prominent publication bias.

DISCUSSION

Current findings

This is the first systematic review, including a meta-analysis so far as we are aware, to show the significant effectiveness of verbal and interactive psychotherapeutic intervention for treating depression among advanced cancer patients. Unfortunately, the effectiveness of other types of non-pharmacological interventions for the treatment of depression could not be analysed because the available data on this topic was insufficient.

Our findings suggest that the effects of psychotherapy are almost comparable to those obtained in antidepressant pharmacotherapy studies in general psychiatry settings (Bech 2000). On the other hand, this effect was not consistent with a previous meta-analysis of 17 clinical trials that investigated the effect of psychological interventions on depression in cancer patients (Sheard 1999). This previous meta-analysis indicated an effect size of 0.19, suggesting a clinically weak or negligible effect. Since the subjects of the majority of the studies included in this previous meta-analysis were not advanced cancer patients and most of the studies had selected their patient populations based on cancer diagnosis, rather than on diagnostic or psychological criteria, or both, differences in the prevalence of clinical depression may be one possible explanation for the discrepancy between their meta-analysis and ours. In other words, since depression is common in patients with advanced cancer (*see* 'Background'), this difference may account for the different findings regarding the effect of the intervention.

Regarding the types of verbal and interactive psychotherapeutic interventions that were included in the meta-analysis, four of the six psychotherapeutic approaches utilized supportive therapy. Probably because of the nature of the study subjects (i.e., people suffering from incurable cancer), all of the approaches involved some form of techniques dealing with the impact of life-threatening disease on patients' lives, including issues of 'dying' or 'existence', or both, in addition to general support (Spiegel 1978; Yalom 1977). In addition, one of the most prominent characteristics of these four studies was the fact that the interventions essentially continued until the patients' deaths. On the other hand, specific types of psychotherapy, especially cognitive behavioural therapy, are widely recommended for the treatment of psychological distress among cancer patients; however, our systematic review highlights the need for more well-designed clinical trials to clarify the effectiveness of cognitive behavioural therapy on depression in patients with advanced cancer.

The findings with regard to anxiety and general psychological distress were similar to those for depression, although the results for anxiety did not reach statistical significance. These findings suggest that the psychotherapy may be useful for ameliorating a broad range of psychological distress, with the exception of anxiety experienced by advanced cancer patients.

Clinical implications and future research

The present findings suggest that the depression experienced by advanced cancer patients, who are well-known to be at risk for developing depression or clinically profound psychological distress, or both, can be effectively ameliorated by psychotherapeutic intervention. Although our review could not clarify the cost effectiveness of psychotherapeutic interventions for patients with advanced cancer, and the fact that long-term continuous interven-

tions requiring trained mental health professionals may not be easy to provide for all patients, our findings suggest that psychological interventions should be combined with routine patient care for the treatment of patients with advanced cancer. At the same time, clarifying the cost-effectiveness of psychotherapy and developing cost-effective interventions for treating depression among advanced cancer patients may be important future tasks.

Some relevant questions remain concerning the effectiveness of psychotherapy on depression among patients with incurable cancer. First, because most studies included in the meta-analysis investigated the impact of the interventions just after or during the process of continuous treatment, or both, the persistent effects of the completed interventions were unclear. Second, because most of the subjects were not clinically diagnosed as having depression, the effectiveness of psychotherapy for the treatment of clinical depression could not be clarified in this review. These clinically important issues should be addressed in future studies.

Finally, we would like to comment on the study quality of the psychological interventions. As reported in the previous reviews, the quality of most of the studies was problematic (Newell 2002; Williams 2006). However, given the difficulty of conducting clinical trials in this population, such as in palliative care settings and of evaluating the quality of clinical trials for psychological interventions (Penrod 2004), novel and realistic quality assessment systems may be needed for studies focusing on patients with advanced cancer.

Methodological advantages of this study

This systematic review has several major strengths. Firstly, we performed systematic and comprehensive literature searches for relevant studies, whereas previous studies contained several major flaws in their methodology, including a language bias (e.g., typically only English papers), and the combination of randomised and non-randomized clinical trials. Second, the *a priori* planned heterogeneity and sensitivity analyses indicated that the results of the analyses were quite robust.

Limitations of this study

Our review also has some limitations. First, the reviewed studies generally had small sample sizes, and only a small number of studies (n = 6) were included in the meta-analysis. These factors may limit the validity of our findings. The existence of a possible outcome reporting bias cannot be negated (Chan 2005; Furukawa 2007). Secondly, although the use of data imputation for missing standard deviations of change scores was found to be valid in one study dealing with pharmacotherapy for depression (Furukawa 2006), whether this procedure was valid in our study sample was not confirmed. Thirdly, while this review included studies on the treatment of depression among advanced cancer patients, the results may not be applicable to advanced cancer patients with clinically diagnosed depression. Additionally, although this study also included meta-analyses for anxiety and general psychological distress, these findings were subsidiary and inconclusive. Finally, because the subjects' physical status (e.g., physical functioning, estimated survival) were not clearly defined *a priori* and the participants were at least not critically terminally ill (i.e. an estimated survival period of less than a few months), the findings may not be applicable to end-stage cancer patients who are nearing death.

Despite these limitations, the obtained findings about the usefulness of psychotherapy for ameliorating depression in advanced cancer patients deserve important consideration, and future studies to investigate and clarify the usefulness of psychotherapy for treating clinically diagnosed depression in terminally ill patients are warranted.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from RCTs of moderate quality suggests that psychotherapy is useful for treating depressive states in advanced cancer patients although little evidence supports the effectiveness of psychotherapy for patients with clinically diagnosed depression including major depressive disorder. The effects of psychotherapy are almost comparable to those observed in antidepressant pharmacotherapy studies of major depressive disorders in general psychiatry settings. Regarding the types of verbal and interactive psychotherapeutic interventions, the most common approach was long-term continuous supportive therapy, typically until the patients' deaths. Although our review could not clarify the cost effectiveness of psychotherapeutic interventions for patients with advanced cancer and considering that long-term continuous interventions requiring trained mental health professionals may not be easy to provide for all patients, our findings suggest that psychological interventions should be combined with routine patient care for the treatment of patients with advanced cancer.

Implications for research

The continuing effects of the completed interventions and the effectiveness of psychotherapy for the treatment of clinical depression should be addressed in future studies. In addition, clarifying the cost-effectiveness of psychotherapy and developing cost-effective interventions for the treatment of depression among advanced cancer patients are also important future tasks. Specific types of psychotherapy, especially cognitive behavioural therapy, are widely recommended for the treatment of psychological distress among cancer patients; however, our systematic review highlights the need for more well-designed clinical trials to clarify the effectiveness of cognitive behavioural therapy on depression in patients with advanced cancer. The effectiveness of psychotherapy for treating depression in end-stage cancer patients who are nearing death should also be investigated. Finally, given the difficulty of conducting clinical trials in palliative care settings and of evaluating the quality of clinical trials for psychological interventions,

novel and realistic quality assessment systems may be needed for studies focusing on patients with advanced cancer.

POTENTIAL CONFLICT OF INTEREST

None known.

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