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# Exploring the perceived changes and the reasons why expected outcomes were not obtained in individual levels in a successful regional palliative care intervention trial: an analysis for interpretations

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## Abstract

**Context** The Japan Outreach Palliative Care Trial of Integrated Model (OPTIM) study, a mixed-methods study to evaluate the effects of a comprehensive regional palliative care program, revealed that the program provided broad positive outcomes at the regional level: increased home death, palliative care use, patient- and family-reported qualities of care, and health care professionals' difficulties. Not all participants however obtained positive outcomes and thus exploring the reasons why expected outcomes were observed in individual levels could be of value.

**Aims** The primary aims were to explore why expected outcomes were not obtained in individual participants, and the

perceived changes in daily practices of physicians and nurses were explored.

**Subjects and methods** Postintervention questionnaire survey on 857 patients, 1,137 bereaved family members, 706 physicians, and 2,236 nurses were analyzed.

**Results** The reasons for not achieving home deaths included unexpected rapid deterioration, caregivers unavailable, concerns about adequate responses to sudden changes, and physical symptoms uncontrolled, while lack of physician availability at home and lack of information from physicians were less frequently reported. The reasons for not receiving specialized palliative care services were the lack of recommendations from physicians and no information about

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palliative care services. The reason for evaluating the quality of palliative care as not high was that clinicians tried to relieve symptoms, but there were limited effects and insufficient time. Many physicians and nurses reported that they became more aware of palliative care, that the availability of palliative care specialists and knowledge about palliative care improved, and that they cooperated with other regional health care providers more easily.

**Conclusion** The OPTIM study seemed to succeed in optimizing physician availability at home, improves physician information about home care, achieved maximum efforts to relieve patient distress by clinicians, and increased communication among regional health care professionals. To achieve further better outcomes, multiple interventions to the health care system to be performed on the basis of a comprehensive regional palliative care program are proposed.

**Keywords** Palliative care · Community · Home death · Barrier · Quality of care

## Introduction

Home deaths, the use of palliative care services, and quality of palliative care are among important outcomes in palliative care. To date, multiple intervention studies investigated whether a specific program actually leads to better outcomes in the location of death, use of palliative care services, and quality of life [1–7]. These outcome studies, however, when the intervention failed to demonstrate beneficial effects overall or for some individuals, did not explore the reasons why these outcomes were observed. Factors potentially contributing to the achievement of these outcomes were explored in survey studies, such as determinants of home death and barriers to referral to specialized palliative care services [8–12]. Exploratory analyses along with intervention studies are recently recommended to identify why the expected outcomes were or were not observed [13, 14].

More recently, the Japan Outreach Palliative Care Trial of Integrated Model (OPTIM) study revealed that a comprehensive regional palliative care program provided broad positive outcomes [15–17]. In this intervention study, a comprehensive regional palliative care program to optimize the existing resources achieved broad positive outcomes at the regional level: increased home death, palliative care use, patient- and family-reported qualities of care, and decreased health care professionals' difficulties. Obviously, not all participants obtained positive outcomes, and we believe that exploring the reasons why expected outcomes were not obtained in individual levels is of value to obtain insight for better interpretation of the results of the regional palliative care program.

The primary aim of this study was to explore the reasons why patients did not die at home, did not receive palliative care services, and did not evaluate the quality of palliative care as high for individual levels in a successful regional intervention study. Additional aim was to clarify the perceived changes in daily practices of physicians and nurses during the study periods.

## Subjects and methods

This is an analysis of a region-based palliative care intervention trial: Japan OPTIM study [15–17]. In the postintervention questionnaire surveys, we asked the patients, bereaved family members, physicians, and nurses about the potential reasons why patients did not die at home, did not receive palliative care services, and did not evaluate the quality of palliative care as high, in addition to perceived changes in daily practices of physicians and nurses during the study periods. The study methodology was described in detail in the methodology paper [16]. Ethical and scientific validity was confirmed by the institutional review board of this study and of all participating hospitals.

## Overview of the OPTIM study [17]

This study was performed in four regions of Japan. We obtained preintervention data for outcomes before or in early phase of the intervention period and postintervention data after or later phase of the intervention periods. The intervention program was implemented from April 2008 to March 2011. The primary end points were home death, use of a palliative care service, and patient-reported and bereaved family-reported qualities of palliative care. Intervention is a comprehensive program covering four areas: (1) to improve the knowledge and skills of palliative care, (2) to increase the availability of specialized palliative care services for community patients, (3) to coordinate community palliative care resources, and (4) to provide appropriate information about palliative care to the general public, patients, and families. We designed all interventions so they did not require a fundamental change in the health care system, that is, to optimize the existing health care resources within the region. After interventions, the percentage of home deaths increased from 6.8 to 10.5 %, and this increase was significantly greater than that in national data. Moreover, 88 % of the family members confirmed that patients who died at home had preferred home death, and the care burden showed no significant increase. The ratio of patients who received palliative care services increased significantly. The patient- and family-reported qualities of care were significantly better after intervention (effect size, 0.14 and 0.23). Physician-

and nurse-reported difficulties, especially regarding communication and coordination, decreased significantly (effect size, 0.52 and 0.59). Accompanying qualitative analysis identified participant's greatly emphasized improved communication and cooperation among regional health care professionals.

## Subjects

For this analysis, all data from 857 patients, 1,137 bereaved family members, 706 physicians, and 2,236 nurses from postintervention surveys were used. Patients bereaved family members, physicians, and nurses were sampled throughout the region as they were nearly representative sample.

### Patients

Inclusion criteria were (1) adults with a metastatic or recurrent cancer of the lung, esophagus, stomach, colon, rectum, pancreas, liver, biliary system, kidney, prostate, bladder, breast, ovary, or uterus; (2) outpatient visits to the oncology or each specialty division; and (3) the patient had been informed of the malignancy. Exclusion criteria include (1) inability of the patient to complete the questionnaire (dementia, cognitive failure, psychiatric illness, language difficulty, or visual loss), (2) severe emotional distress of the patient as determined by the principal treating physicians, and (3) unable to complete the questionnaire due to poor physical condition.

### Bereaved families

Inclusion criteria for bereaved family members were (1) an adult family member of an adult patient with cancer who had died in a health care institution or at home (one family member listed as a principle caregiver on the medical record was selected for each patient); (2) the cancer was a primary tumor of the lung, esophagus, stomach, colon, rectum, pancreas, liver, biliary system, kidney, prostate, bladder, breast, ovary, or uterus; (3) the patient had received medical treatment from the institution on three or more days; and (4) the patient had been informed of the malignancy. Exclusion criteria include (1) incapacity to complete the questionnaire (dementia, cognitive failure, psychiatric illness, language difficulty, or visual loss), (2) severe emotional distress of the family as determined by the principal treating physicians, (3) treatment-associated death or death from commodity, (4) death in intensive care units, and (5) unavailable family member. Families were surveyed 6 to 12 months after patient's death.

### Physicians and nurses

Inclusion criteria were (1) hospital physicians and nurses working in cancer-related specialties, a representative physician of general practice clinics, or all district nurses; and (2) clinical experience of 3 years or longer. Subjects are excluded if they have treated no cancer patients during the most recent year.

### Measurements

We generated question items on the basis of the existing literature [8–12], discussion among the authors, and interviews on 20 health care professionals. The questions focused on the potential reasons why expected outcomes were not obtained for each individual and perceived changes during the study periods. We prepared “the others” item with free comments for all questions because there might be other reasons we had assumed and to enable qualitative analyses further. To obtain the views from both physicians/nurses and patients/families, the questions in the physician questionnaire were designed as corresponding to those in the patient questionnaire, e.g., “asked the patients about their preferred place of death as much as possible” (in the physician/nurse questionnaire) vs. “no information from physicians” (in patient/family questionnaire). Pilot test was performed on 20 physicians and nurses; no formal reliability and validity testing was performed.

### Reasons why patients did not die at home

We first asked bereaved family members who reported that patients did not die at their preferred place where the patient had wanted to die (home, palliative care unit, hospital, and others). We then asked family members who reported that patients had wanted to die at home but actually died at other places about the potential reasons, including (1) caregivers unavailable, (2) unexpected rapid deterioration, (3) physical symptoms uncontrolled, (4) home-visit physicians or nurses unavailable, (5) concerns about adequate responses to sudden changes, (6) belief that the patient would become better, and (7) no information from physicians. Family members were asked to choose all relevant items.

We also asked all physicians and nurses about the degree of agreement for each statement based on their clinical experience during the study period based on a 5-point Likert-type scale from disagree to agree (1) patients and/or families did not desire death at home even if recommended, (2) caregivers unavailable for patients who wanted to die at home, (3) unexpected rapid deterioration, (4) physical symptoms uncontrolled, (5) home-visit physicians or nurses unavailable, (6) tried to respond to patients' desire to stay

at home as much as possible, and (7) asked the patients about their preferred place of death as much as possible.

#### Reasons why patients did not receive palliative care services

We first asked the patients and family members who reported “strongly disagree”, “disagree,” or “slightly disagree” for the Good Death Inventory item “free from physical discomfort” about whether they received specialized palliative care services [15]. We then asked those who did not receive palliative care services about the potential reasons, including (1) minimal interference with daily life, (2) no recommendation from physicians, (3) no information about how to consult palliative care services, (4) explained to that symptoms would continue only for short periods, (5) time and cost spent for consultation, (5) negative image of palliative care services (palliative care is only for dying patients), and (6) long-standing symptoms before diagnosis of cancer. Respondents were asked to choose all relevant items.

We also asked physicians who reported that they consulted no patients regarding palliative care services during this study periods about the reasons for no referral, including (1) encountered no patients with unpalliated symptoms, (2) encountered patients with unpalliated symptoms but was unaware that palliative care services were available in the region, (3) burdensome procedures to receive consultation, (4) cannot easily seek consultation, and (5) patients and/or family did not want services when recommended.

#### Reasons why the patients did not evaluate quality of palliative care as high

We asked patients and bereaved family members who reported “improvement is necessary”, “considerably necessary,” or “highly necessary” for the Care Evaluation Scale item “doctors tried to relieve physical discomfort” about the reasons [15] including (1) physicians did not respond at all to the patient symptoms, (2) physicians tried to relieve symptoms but had limited effects, (3) no opportunity to talk with physicians, (4) physicians were reluctant to talk, (5) insufficient time, and (6) different physicians on every visit. Patients were asked to choose all relevant items.

We also asked all physicians and nurses about the level of agreement for each statement based on their clinical experience during the study periods with the 5-point Likert-type scale from disagree to agree (1) insufficient time for responses to patient needs acknowledged, (2) tried to relieve symptoms but limited effects, (3) patients and/or families did not want symptom palliation even if recommended, (4) tried to relieve symptoms as much as possible, and (5) asked the patients if they had symptoms or concerns.

#### Perceived changes in physicians and nurses

We asked all physicians and nurses about the level of agreement for each statement using the 5-point Likert-type scale from disagree to agree about the perceived changes in their clinical experience during the study period. Items are listed in Table 4.

#### Statistical analyses

Analyses were mainly descriptive, and 95 % confidence intervals were calculated. The frequency of the participants who chose “the others” was small (less than 5 %), and we did not calculate the frequencies for the others responses. Perceived changes were compared among hospital physicians, general practice physicians, hospital nurses, and district nurses using analysis of variance with the Scheffe test as a post hoc test. All statistical procedures were performed using the IBM SPSS statistical software package 19.

## Results

#### Why patients did not die at home?

Among all bereaved family members, 315 families (28 %) reported that patients did not die in their preferred place (Table 1). Of them, the preferred places of death were homes (76 %,  $n=239$ ), hospitals (6.7 %,  $n=21$ ), palliative care units (4.8 %,  $n=15$ ), others (3.8 %,  $n=12$ ), and unsure (8.9 %,  $n=28$ ). The patients whose family members reported that they had wanted to die at home but actually did not thus accounted for 21 % (239/1,137) of all deaths.

The main reasons for not achieving home deaths included unexpected rapid deterioration, caregivers unavailable, physical symptoms uncontrolled, and concerns about adequate responses to sudden changes. Less than 10 % of the families listed lack of physician availability at home and lack of information from physicians. More than 70 % of the physicians reported that they tried to ask the patients about their preferred place of death and respond to patient desire to stay at home.

#### Why patients did not receive palliative care services?

Among the 857 patients and 1,137 families, 111 patients (13 %) and 345 families (30 %) reported slightly disagree, disagree, or strongly disagree for the item “free from physical distress” (Table 2). Of them, 20 patients and 114 families reported that they had received specialized palliative care services, and 34 patients and 108 families reported that they were unsure. Thus, the remaining 57 patients (51 %) and 123 families (36 %) reported that they did not receive specialized

**Table 1** Reasons why patients did not die at home

	Families ( <i>n</i> =239)		Physicians ( <i>n</i> =706)		Nurses ( <i>n</i> =2,236)	
	% (95 % CI)	n	% (95 % CI)	n	% (95 % CI)	n
Caregivers unavailable	20 % (15, 25)	47	37 % (33, 40)	259	36 % (34, 48)	800
Unexpected rapid deterioration	45 % (39, 52)	108	31 % (28, 35)	219	42 % (39, 44)	928
Home-visit or nurses physicians unavailable	6.3 % (4, 10)	15	13 % (11, 16)	92	8.1 % (7, 9)	180
Physical symptoms uncontrolled	48 % (42, 54)	115	16 % (14, 19)	116	25 % (23, 26)	551
Concerns about adequate responses to sudden changes	42 % (36, 49)	101	NA		NA	
Belief that the patient would become better	15 % (11, 20)	35	NA		NA	
No information from physicians	6.3 % (4, 10)	15	NA		NA	
Patients and/or families did not desire death at home	NA		38 % (35, 42)	269	35 % (33, 37)	784
Tried to respond to patient need to stay at home	NA		78 % (74, 81)	548	69 % (67, 71)	1,545
Asked the patients about their preferred place of death	NA		71 % (67, 74)	499	53 % (51, 55)	1,193

For physicians and nurses, values are total number of responses of agree or slightly agree  
*CI* confidence intervals

palliative care services. Of the 706 physicians, 199 (28 %) reported that they had consulted no patients regarding palliative care services during this study period.

The main reasons for not receiving specialized palliative care services observed in patients and families were the lack of recommendations from physicians and no information about how to consult palliative care services.

In addition, 40 % of the patients listed minimal interference with daily life and 25 % received an explanation that symptoms would continue only for short periods as a reason. About 60 % of the physicians reported that they encountered no patients with unpalliated symptoms, and 15 % reported that they were unaware palliative care services were available.

**Table 2** Reasons why patients did not receive palliative care services

	Patients ( <i>n</i> =57)		Families ( <i>n</i> =123)		Physicians ( <i>n</i> =199)	
	% (95 % CI)	n	% (95 % CI)	n	% (95 % CI)	n
Minimum interference with daily life	40 % (29, 53)	23	11 % (6, 17)	13	NA	
No recommendation from physicians	33 % (22, 46)	19	56 % (47, 65)	69	NA	
No information about how to consult palliative care services	33 % (22, 46)	19	28 % (21, 37)	35	NA	
Explained that symptoms would continue only for short periods	25 % (15, 37)	14	0		NA	
Time and cost for consultation	12 % (6, 23)	7	0.8 % (0, 5)	1	NA	
Negative image of palliative care services	12 % (6, 23)	7	14 % (9, 21)	17	NA	
Long-standing symptoms before cancer	11 % (5, 21)	6	3.3 % (1, 8)	4	NA	
Encountered no patients with unpalliated symptoms	NA		NA		62 % (55, 69)	124
Being unaware palliative care services were available	NA		NA		15 % (10, 20)	29
Burdensome procedures for consultation	NA		NA		7.5 % (5, 12)	15
Cannot easily seek consultation	NA		NA		7.0 % (4, 12)	14
Patients and/or families did not want services when recommended	NA		NA		3.0 % (1, 6)	6

For physicians, values are total number of responses of agree or slightly agree  
*CI* confidence intervals

Why the patients did not evaluate the quality of palliative care as high?

Among the total of 857 patients and 1,137 families, 132 patients (15 %) and 210 families (18 %) evaluated palliative care as improvement necessary, considerably necessary, and highly necessary, and, of these, 62 patients and 153 families gave valid answers as to why (the remainder gave no responses, probably because of the complex questionnaire layout) (Table 3).

The main reasons for evaluating the quality of palliative care as not high were clinicians tried to relieve symptoms but had limited effects and insufficient time. This result was consistently observed across patients, families, physicians, and nurses.

#### Perceived changes of physicians and nurses

The majority of physicians and nurses across all working situations reported that they became more aware of palliative care and valued multidisciplinary teams (Table 4). Half or more participants also reported that the availability of palliative care specialists and knowledge about palliative care improved; and 80 % of the hospital physicians reported that they consulted a palliative care team earlier than before. About 30 to 50 % of all respondents reported that they cooperated with other regional health care providers more easily. About half of the general practice physicians reported that they became to accept caring for cancer patients at home more confidently. In general, these perceived changes were more often reported by the district nurses, followed by hospital physicians, rather than general practice physicians and hospital nurses.

## Discussion

The strengths of this study are twofold: one is clarification of the potential reasons why the expected outcomes were not achieved in individual levels based on the comprehensive assessment of patients, families, physicians, and nurses; and the other is the clarification of physician- and nurse-perceived changes during the study periods. Both contribute to a better understanding of the overall results of this regional intervention trial.

#### Why patients did not die at home?

This study revealed that about 30 % of the patients died in places other than their preferred place, and they had mostly wanted to die at home. The reasons reported were unexpected rapid deterioration, caregivers unavailable, physical symptoms uncontrolled, and concerns about adequate responses to sudden changes. On the other hand, the lack of physician availability at home and insufficient information about home care were not listed as major reasons. These findings suggest that the intervention was likely to succeed in increasing physician availability at home and improved information about home death potentially through region-wide support for general practice physicians and education about the importance of the preferred place of death for health care professionals. The findings that half of the general practice physicians and district nurses reported that they were more likely to accept caring for cancer patients at home more confidently through increased knowledge and support, and the fact that 71 % of the physicians reported that they had asked the patients about their preferred place of death supports this interpretation. The identified reasons of unexpected

**Table 3** Reasons why patients did not evaluate the quality of palliative care as high

	Patients ( <i>n</i> =62)		Families ( <i>n</i> =153)		Physicians ( <i>n</i> =706)		Nurses ( <i>n</i> =2,236)	
	% (95 % CI)	<i>n</i>	% (95 % CI)	<i>n</i>	% (95 % CI)	<i>n</i>	% (95 % CI)	<i>n</i>
Tried to relieve symptoms but limited effects	65 % (52, 75)	40	66 % (58, 73)	101	24 % (21, 28)	171	36 % (34, 38)	807
Insufficient time	29 % (19, 41)	18	29 % (23, 37)	45	28 % (25, 32)	198	41 % (39, 43)	911
Physician reluctant to talk	18 % (10, 29)	11	12 % (8, 18)	18	NA		NA	
Physicians did not respond at all	8.1 % (3, 18)	5	5.2 % (3, 10)	8	NA		NA	
No opportunity to talk with physicians	8.1 % (3, 18)	5	10 % (6, 16)	15	NA		NA	
Different physicians at every visit	4.8 % (2, 13)	3	2.0 % (0, 4)	3	NA		NA	
Patients and/or family did not want services	NA		NA		7.2 % (6, 9)	51	9.8 % (9, 11)	220
Tried to relieve symptoms as much as possible	NA		NA		75 % (72, 78)	530	72 % (70, 74)	1,614
Asked the patients if they had symptoms or concerns	NA		NA		75 % (72, 78)	532	74 % (72, 76)	1,648

For physicians, values are total number of responses of agree or slightly agree  
*CI* confidence intervals

**Table 4** Perceived changes of physicians and nurses in daily practice

	Hospital physicians ( <i>n</i> =486)	General practice ( <i>n</i> =220)	Hospital nurses ( <i>n</i> =2,026)	District nurses ( <i>n</i> =210)	<i>P</i>
Become more aware about palliative or home care in daily practice	75 %, 364	53 %, 117	68 %, 1,377	82 %, 173	<0.001 <sup>a</sup>
Respect patients' hopes, feelings, and values	79 %, 386	69 %, 152	82 %, 1,658	88 %, 184	<0.001 <sup>e</sup>
Pay greater attention to families	75 %, 366	69 %, 151	81 %, 1,638	88 %, 184	<0.001 <sup>e</sup>
Recognize greater value of interdisciplinary team	84 %, 406	61 %, 135	84 %, 1,693	88 %, 184	<0.001 <sup>c</sup>
More specialists available for consultation in palliative care	77 %, 373	45 %, 98	68 %, 1,383	56 %, 117	<0.001 <sup>b, c</sup>
Consult palliative care team earlier	81 %, 395	NA	74 %, 1,496	NA	<0.001
More accurate knowledge about palliative care through education programs	64 %, 312	49 %, 107	51 %, 1,041	63 %, 132	<0.001 <sup>f, g, h</sup>
Cooperate with other health care providers in the region more easily through getting to know persons involved in palliative care	47 %, 229	36 %, 79	30 %, 609	47 %, 99	<0.001 <sup>g, h</sup>
More opportunities to meet multidisciplinary professionals beyond facilities	39 %, 189	32 %, 70	33 %, 667	50 %, 105	<0.001 <sup>g, i</sup>
Provide more specific information through getting to know resources	50 %, 245	41 %, 91	29 %, 587	46 %, 96	<0.001 <sup>d</sup>
More recognize that cancer patients could die at home if desired	65 %, 315	45 %, 98	66 %, 1,337	84 %, 176	<0.001 <sup>c, e</sup>
More routinely determined procedures for sudden changes in advance for patients discharge to home	52 %, 253	39 %, 86	43 %, 874	77 %, 161	<0.001 <sup>e, h</sup>
Plan hospital care to make it available and simple at home	66 %, 320	NA	62 %, 1,265	NA	0.19
Accept caring for cancer patients at home more confidently through increased knowledge and support	NA	40 %, 89	NA	65 %, 137	<0.001

Values are total number of responses of agree or slightly agree

NA not available

<sup>a</sup> Among all professions

<sup>b</sup> Hospital physician (HP) vs. all other professions

<sup>c</sup> GP vs. all other professions

<sup>d</sup> Hospital nurse (HN) vs. all other professions

<sup>e</sup> District nurse (DN) vs. all other professions

<sup>f</sup> HP vs. GP

<sup>g</sup> HN vs. DN

<sup>h</sup> HP vs. HN

<sup>i</sup> GP vs. DN

rapid deterioration and caregivers unavailable are understandable because no intervention is specifically aimed to facilitate an education program about survival estimation for physicians and to enhance informal caregiver resources [16]. As multiple studies have demonstrated that clinicians are significantly likely to overestimate the prognosis of terminally ill patients [18] and that the presence of formal and informal caregivers is one of the most important determinants of home death [8, 9], systematic efforts to improve physician prognostication, such as the dissemination of validated prognostic tools and facilitating proactive strategies throughout the region [19–21], and reconstructing social resources to optimize formal and informal caregivers, are necessary to achieve more home death. Against uncontrolled physical symptoms as a reason for discontinuing staying at home, this study encouraged community palliative

care team and a continuing effort to establish community palliative care services is highly valuable [22–24]. To lessen concerns about adequate responses to sudden changes, the health care system of 24-h 7-day service is more encouraged.

#### Why patients did not receive palliative care services?

This study revealed that 30 % of terminally ill patients might suffer from considerable levels of symptoms, and 30 % to half did not receive palliative care services. For outpatients, the frequency of unpalliated symptoms was generally low, and patient-reported reason for not receiving palliative care services was minimal interference with daily life, which are understandable, because this population showed a generally good performance status, and their symptoms were likely to

be transient associated with anticancer treatment. Contrary to previous surveys [10–12], this study revealed that a negative image about palliative care in patients and families was not reported as the main reason for nonreferrals. The findings from the qualitative analyses that the intervention improved perception about palliative care of core health care professionals [17], and that more than 80 % physicians surveyed reported that they referred patients to a palliative care team earlier than before, support the idea that intervention succeeded in improving general perceptions of palliative care of health care professionals. On the other hand, the main reasons for no use of palliative care services by patients and families included no recommendation from physicians and no information about how to consult palliative care services, and the majority of the physicians who did not use specialized palliative care services reported that they encountered no patients with unpaliated symptoms. On considering previous findings that the assessment of symptom intensity demonstrated low-level agreement between physicians and patients [25], and physician recommendation is one of the strongest determinants in referral to specialized palliative care services [10], this can be interpreted as the physician's inability in identifying patients who receive some benefits from palliative care services and/or a lack of awareness of palliative care services available in the region. Potential resolutions to overcome this barrier may be using a simple visible and routine need assessment tool with clear instruction of when and how to consult palliative care services in the region [26, 27].

#### Why patients did not evaluate the quality of palliative care as high?

This study revealed that about 20 % of patients and families evaluated the quality of palliative care as still requiring improvement. The major reasons were clinicians actually tried to relieve symptoms but limited effects and insufficient time; that is, negative attitudes of clinicians were rarely reported by patients and families. The majority of physicians and nurses surveyed reported that they respected patients' hopes and paid greater attention to families. A possible interpretation of this result is that physicians and nurses actually made maximum efforts to relieve patients' distress within the limited time allowed, but patient distress often demonstrated no apparent improvement due to (1) the refractory nature of the symptom (e.g., fatigue, anorexia, neuropathic or incidental pain); (2) nonreferral to palliative care services, resulting in failure to optimize symptom palliation; or 3) lack of time to address complex psychological, social, and spiritual issues, resulting in unsatisfactory outcomes. Potential systematic resolutions include (1) research to identify effective palliative treatment of difficult symptoms

[28–30] and (2) ensuring enough time for each clinician to address patients' concerns.

#### Physician- and nurse-perceived changes during the study period

The findings were generally consistent with the accompanying qualitative study and confirmed some generalizability [17]. The value of this quantitative study is clarifying the relative frequency of each perceived change of health care professionals. Physicians and nurses reported increased perception of the importance of palliative care most frequently, followed by the improved availability of palliative care specialists and improved knowledge about palliative care, and improved perception about home care. Of interest is that improved communication and cooperation among regional health care professionals are relatively less frequent. This is in somewhat contrast to the finding of the accompanying qualitative study that strongly emphasized improved communication and cooperation [17]. The interpretation of this finding is that the regional palliative care program did improve communication and cooperation among health care professionals, and the effect was strongly observed especially in people in a leadership role, rather than clinicians working in general positions.

Despite the strength of this study regarding the success in obtaining data from comprehensive data sources at regional levels, this study has several limitations. First, response bias was not so high and no formal testing of the questionnaire's reliability and validity was performed. Second, substantial number among the patients and family members who reported disagree for the item free from physical distress answered that they were unsure whether they received specialized palliative care services (34/111, 108/345, respectively). This is because (1) we had decided not to combine patient-reported data with medical record data (i.e., use of palliative care services) due to technical difficulties, and (2) patients and family members often did not recognize the participation of specialized palliative care services when they provided consultation services (did not directly see the patient and family members). This could make a bias, but we cannot assume the direction of the bias. Third, there were relatively frequent missing values in some questions. This is probably because we had located these additional questions in the last of pages of the questionnaire, distant from the original questions, due to the lack of space. This could be a bias, but we believe that missing occurred randomly and the major results would be the same. Finally, we concluded the intervention was likely to succeed in increasing physician availability at home because the lack of physician availability at home was not listed as the major reason for not staying at home. However, as there are no preintervention data to directly support this, the conclusion needs to be carefully interpreted.

In conclusion, this analysis suggests, to achieve better outcomes, some medical system interventions can be promising on the basis of a comprehensive regional palliative care program: (1) routine proactive care planning based on validated prognosis estimation, (2) reconstructing social resources to increase informal caregivers, (3) establishing formal community palliative care services as easily available and a 24-h 7-day service, (4) using a simple visible and routine-need assessment tool with clear instruction of when and how to consult palliative care services in the region, (5) ensuring enough time for each clinician to address patients' concerns, and (6) research to explore more effective palliative treatment of frequent but difficult symptoms.

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## Impaired mental health among the bereaved spouses of cancer patients

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### Abstract

**Objective:** Few cancer physicians routinely provide bereavement follow-up in clinical practice. The purpose of this study was to identify the prevalence of impaired mental health among the bereaved spouses over several years and explore the indicators for early detection of high-risk spouses during end-of life (EOL) care.

**Methods:** A cross-sectional mail survey was conducted for the bereaved spouses of patients who had died at the National Cancer Center Hospital of Japan. Bereaved spouses with potential psychiatric disorders were identified by the cut-off score of the 28-item General Health Questionnaire. Associated factors of potential psychiatric disorders were explored by logistic regression analysis.

**Results:** A total of 821 spouses experiencing bereavement from 7 months to 7 years returned the questionnaires. Overall mean prevalence of potential psychiatric disorders was 44% (360/821). Bereaved spouses 'under 55 years' (71%) or '2 years after bereavement' (59%) revealed a significantly higher prevalence ( $p < 0.01$ ). Associated factors during EOL care were several characteristics such as 'spouses' history of psychiatric disorder (odds ratio (OR) = 3.19), 'patients' with stomach cancer (OR = 1.87), and 'patients' using psychiatric consultation services (OR = 1.52) as well as spouses' dissatisfaction with EOL care such as 'physicians' treatment of physical symptoms' (OR = 3.44) and 'time spent communicating with patients' (OR = 1.55).

**Conclusions:** Nearly half the bereaved spouses showed potential psychiatric disorders even 7 years after bereavement. Patients' psychological distress, spouses' history of psychiatric disorder, and dissatisfaction with EOL care were indicators of high-risk spouses.

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### Introduction

Conjugal bereavement was the strongest risk factor for depression among elderly community subjects in a meta-analysis of 20 studies (odds ratio (OR) = 3.3) [1] and bereaved spouses showed a significant increase in the risk of depression compared with married people in large cohort studies (1.5-fold, 3.6-fold) [2,3]. In oncology settings, spouses experienced the highest levels of distress among family members at the time of patient death [4] and bereavement brought an increased risk of major depressive disorder [5,6]. Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths (around 13% of all deaths) in 2008 [7]; however, few cancer physicians routinely provide bereavement follow-up in clinical practice [8].

Several longitudinal studies have reported that impaired mental health among the bereaved clearly diminishes over time. The prevalence of major depressive disorder among caregivers of cancer patients was identified by clinical interview: 28% at the time of hospice enrollment, 12% at 6 months after death, and 7% at 1 year after death [5,6]. Depression, anxiety, and grief measured by self-administered questionnaire decreased during the first year after bereavement [9–11] and then remained unchanged over the next year [11]. On the other hand, cross-sectional studies reported that negative effects such as anger, sadness, self-blame, and guilt did not decrease among those who had been bereaved for more than 4 years [12,13] and 25% of the bereaved parents had not worked through their grief even 4–9 years after the loss [14]. However,

these persistent symptoms could not predict the prevalence of potential psychiatric disorders among the bereaved.

Impaired mental health among the bereaved who have lost a relative to cancer is associated with several characteristics of the patients and the bereaved. As for clinical characteristics of cancer patients, 'short duration of hospice enrollment' [5,6], 'intensive end-of-life (EOL) care' [15], and 'ICU death' [16] were associated with impaired mental health among the bereaved. In addition, bereaved characteristics of 'under 65 years' [9], 'female' [5,17,18], 'spouse' [5], 'prior physical symptoms' [5], 'prior depression' [5,9,17], and 'anticipatory grief' [16] were also reported. However, these associated factors are not useful as indicators for early detection of high-risk spouses during EOL care in clinical practice at a hospital even though 90% of cancer patients in Japan die in a hospital [19].

In the present study, the primary purpose was to identify the prevalence of impaired mental health that can be used to predict the prevalence of potential psychiatric disorders among the bereaved who have lost their spouse to cancer. The secondary purpose was to investigate associated factors of the prevalence so that we could suggest the indicators for early detection of high-risk spouses during EOL care.

## Methods

### Study sample

We conducted a cross-sectional mail survey for the bereaved spouses whose partner had died at the National Cancer Center Hospital East (NCCHE). This study was

approved by the Institutional Review Board and Ethics Committee of the National Cancer Center of Japan in January 2009.

First, in January 2009, we found it necessary to identify family members to whom we intended to mail study participation invitations; this was because of a lack of accurate data about marital status in the hospital patient database. Eligibility criteria were (i) patient's primary clinician belonging to the eight divisions cooperating with this study (Hematology, Pancreatic, Head and Neck, Gastric Surgery, Gastrointestinal, Thoracic Surgery, Thoracic Oncology, and Palliative Care), which covered 98% of the patients who died at NCCHE; (ii) patient's data available in the hospital's patient database operating since January 2001; and (iii) patient's death occurring at least 6 months earlier. Exclusion criteria and flow of the study sample are explained in Figure 1.

We matched the demographic characteristics of the deceased cancer patients drawn from the hospital patient database with those of the bereaved spouses based on the completed questionnaires. Respondents' characteristics ( $n=821$ ) showed a lower proportion of males (30%,  $n=242$  vs. 36%,  $n=753$ ,  $p < 0.01$ ) and a shorter duration of bereavement ( $3.0 \pm 1.9$  vs.  $3.2 \pm 2.0$  years,  $p < 0.01$ ) compared with the non-responders ( $n=2081$ ) among the 2902 candidate participants; the difference in values of the deceased patients' characteristics such as age, duration of last hospital admission, place of death, history of usage of psychiatric consultation services, and cancer site was not significant.

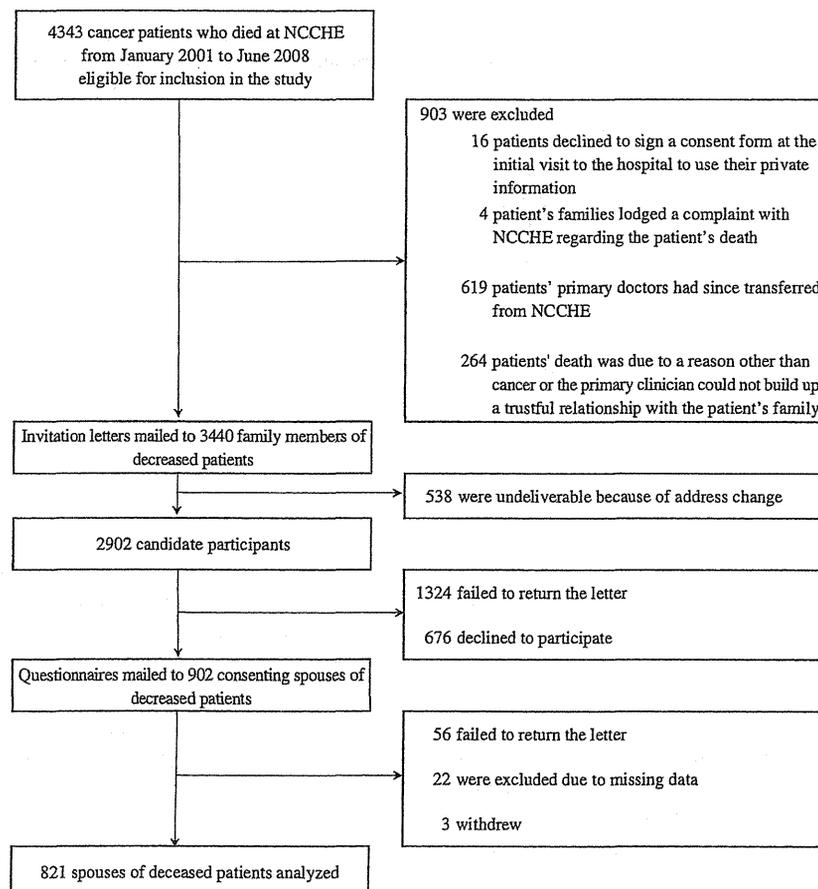


Figure 1. Flow of study sample

Measures

Deceased patients' characteristics

We examined the overall computerized patient database of NCCHE to identify cancer patients' characteristics. Time since cancer diagnosis to death was declared in the questionnaires completed by the bereaved. History of usage of psychiatric consultation services was identified by using the consultation database developed by the Psychiatric Services Division of the NCCHE. This computerized database [20] includes demographic variables and psychiatric disorders of patients who were referred to the Psychiatric Services Division.

Bereaved spouses' characteristics

The questionnaires completed by the bereaved spouses included physical and psychological information such as physical illness under treatment and history of psychiatric disorder prior to their partner's death as well as demographic variables.

Dissatisfaction with EOL care

The bereaved spouses retrospectively reported their dissatisfaction with EOL caregiving (five items) and physician's EOL care (four items) during the month prior to the patient's death using a five-point Likert-type scale (0: very satisfied, 1: fairly satisfied, 2: neutral 3: fairly dissatisfied, 4: very dissatisfied). We rescored each item as 0 (absence of dissatisfaction, 0–2) or 1 (presence of dissatisfaction, 3–4) in this study.

Impaired mental health

The General Health Questionnaire (GHQ), using a four-point Likert-type scale (possible range, 0–3; higher scores indicate impaired mental health), has been widely used to detect persons with nonspecific psychiatric disorders [21]. We used the validated Japanese 28-item version (GHQ28 [22]). Persons with potential psychiatric disorders were identified by the cut-off score of the GHQ scoring method (0-0-1-1; possible range, 0–28; cut-off score, 5/6). This cut-off score showed the best sensitivity and specificity when compared with the ratings of the clinical interview [23,24] and this approach has shown its applicability to the Japanese version [22].

Statistical analysis

Impaired mental health was compared using analysis of variance with the Bonferroni multiple comparison method or *t*-test. Potential psychiatric disorders were compared by using the chi-square test with residual analysis. Variables showing *p*-values < 0.05 in the univariate analysis were entered as independent variables in a multivariate logistic regression analysis with backward elimination to identify associated factors of potential psychiatric disorders.

*P*-values < 0.05 were considered significant and all *p*-values were two-tailed. All statistical analyses were carried out using SPSS ver.12.0J for Windows (SPSS Japan Institute Inc., Tokyo, Japan).

Results

Characteristics of deceased patients/bereaved spouses

Table 1 summarizes the characteristics of the 821 participants experiencing bereavement from 7 months to 7 years.

**Table 1.** Characteristics of deceased patients and bereaved spouses (*n* = 821)

	Mean ± SD	
	(median, range)	<i>n</i> (%)
Deceased patients' characteristics		
Age, years	64 ± 9.0 (65, 32–88)	
Time since cancer diagnosis to death, months	27 ± 29 (16, 1–187)	
Duration of last hospital admission, days	27 ± 29 (17, 1–208)	
Bereaved spouses' characteristics		
Age, years	66 ± 9.0 (66, 32–89)	
Time since bereavement, years	3.0 ± 1.9 (3.0, 0.6–7.2)	
Gender		
Male		242 30
Female		579 70

SD, standard deviation.

In this study, 579 bereaved (70%) were female, 441 patients (54%) died in the Palliative Care Unit, and 629 bereaved (77%) were involved in EOL caregiving 'everyday'.

Prevalence of impaired mental health and potential psychiatric disorders

As shown in Table 2, we estimated the population of bereaved spouses to be 2649 by multiplying the total number of 4343 deceased patients by 0.61, which is the approximate ratio of Japanese cancer patients who have a spouse at the time of death among overall cancer deaths in Japan in 2007 (206,389/336,139)[19]. As a result, the overall sampling rate (estimated) was 31% (821/2,649), and the prevalence of potential psychiatric disorders was 44% (360/821, 95% CI = 40.6–47.4).

With impaired mental health, three-way interaction (age × gender × time) was not significant (*F* (18, 689) = 1.56, *p* = 0.07). Two-way interaction (age × gender: *F* (3, 689) = 2.75, *p* = 0.04) was significant: males 'under 55 years' showed significantly greater prevalence than males '55–64 years' or 'over 75 years' (*F* (3, 214) = 3.66, *p* = 0.01, A0 > A1, A3, *p* < 0.05) and females 'under 55 years' or '55–64 years' showed significantly greater prevalence than females '65–74 years' (*F* (3, 533) = 4.65, *p* < 0.01, A0, A1 > A2, *p* < 0.05). The main effect of time was significant (*F* (6, 689) = 2.71, *p* = 0.01): the bereaved who had lost their spouse '2 years ago' revealed significantly greater prevalence than those who had lost their spouse '4 years ago' with multiple comparison (*F* (2, 738) = 3.31, *p* < 0.01, T2 > T4, *p* < 0.05).

The prevalence of the bereaved varied with age and time: 'under 55 years' (71%) revealed significantly higher prevalence than those '65–74 years' (42%) ( $\chi^2$  (3) = 23.17, *p* < 0.01, A0 > A2, *p* < 0.01) and the bereaved who had lost their spouse '2 years ago' (59%) revealed significantly higher prevalence than those who had lost their spouse '4 years ago' (37%) ( $\chi^2$  (6) = 17.81, *p* < 0.01, T2 > T4, *p* < 0.01). No significant difference was observed between genders ( $\chi^2$  (1) = 1.08, *p* = 0.34).

Factors associated with potential psychiatric disorders

In the univariate analysis, 14 variables were significantly associated with potential psychiatric disorders (*p* < 0.05, Table 3). Table 4 shows the results of a multivariate logistic regression analysis: 'patients using psychiatric consultation

**Table 2.** Prevalence of impaired mental health and potential psychiatric disorders among bereaved spouses of cancer patients

	Year	Group	Deceased patients	Population <sup>a</sup>	Sample	Sample rate	Impaired mental health		Potential psychiatric disorders	
			N	N'		n	%(n/N')	Mean (SD)	n'	%(n'/n)
Total			4343	2649	821	31	7.17 (6.79)	360	44	40.6–47.4
Age										
	–54	A0			75		(9.95) 6.59	53	71	60.4–81.0
	55–64	A1			232		7.65 (6.77)	118	51	44.5–57.3
	65–74	A2			339		6.37 (6.68)	141	42	36.4–46.9
	75–	A3			109		6.62 (6.77)	46	42	32.9–51.5
Gender										
Male			1494	911	220	24	6.93 (6.65)	98	45	37.9–51.1
Female			2849	1738	538	31	7.27 (6.86)	262	49	44.5–52.9
Time since bereavement										
	<1	T0	258	157	55	35	8.67 (7.41)	30	55	41.3–67.7
	<2	T1	668	407	133	33	7.79 (7.38)	66	50	41.1–58.1
	<3	T2	611	373	134	36	8.60 (6.92)	79	59	50.7–67.3
	<4	T3	616	376	111	30	6.00 (6.29)	44	40	30.5–48.7
	<5	T4	643	392	96	24	5.48 (6.05)	35	37	26.9–46.1
	<6	T5	671	409	108	26	6.74 (6.56)	45	42	32.4–51.0
	≥6	T6	876	534	108	20	6.97 (6.55)	55	51	41.5–60.3

Some percentages do not add up to 100% because of missing data.

SD, standard deviation; CI, confidence interval.

<sup>a</sup>Population was estimated by multiplying the number of deceased patients (N) by 0.61, which is the approximate ratio of Japanese cancer patients who have a spouse at the time of death among overall cancer deaths in Japan in 2007.

services' (OR = 1.52), 'patients with stomach cancer' (OR = 1.87), and 'bereaved with a history of psychiatric disorder' (OR = 3.19) were significantly associated factors among the characteristics of patients/bereaved prior to the patient's death. Additionally, 'time spent communicating with patients' (OR = 1.55) and 'physician's treatment of physical symptoms' (OR = 3.44) were significantly associated factors among the bereaved spouses' dissatisfaction with EOL care during the final month.

## Discussion

In this study, we identified a considerably high prevalence of potential psychiatric disorders among the bereaved (44% of total respondents). Patients' psychological distress, bereaved spouses' history of psychiatric disorder, and dissatisfaction with EOL care were indicators for early detection of high-risk spouses prior to the patient's death.

Our results indicated that, even 7 years after losing their spouse, a significant number of the bereaved have potential psychiatric disorders (37–59%). This is a higher prevalence than that of consecutive patients in general practice in Britain (35%) [25] and is three-fold higher than that of a healthy sample in Japan (14%) [22]. We discuss this high prevalence from two aspects of the results. First, more than half the spouses within less than 3 years since bereavement showed potential psychiatric disorders. This high prevalence might be inflated by normal grief, a common psychological reaction among the bereaved. Our results support those of the previous studies in which prevalence decreased during the first year after bereavement [9–11]. However, our results do not support previous results where prevalence remained unchanged over the second year [11]. This discrepancy might partly be because of spouses participating in the Japanese Buddhist rite of *sankaiki* where bereaved families gather together on the second anniversary of the death and reminisce about the deceased. This mourning ceremony might increase

the psychological distress of the bereaved by triggering negative psychological states such as yearning, an unfulfilled desire to reunite with the deceased. Second, around 40% of the respondents whose bereavement was 3–7 years earlier showed potential psychiatric disorders. Even though their psychological distress might have eased somewhat after the mourning ceremony in the second year, the prevalence of both impaired mental health and potential psychiatric disorders was considerably high among the spouses after bereavement. This result could be because of subsequent physical problems of the bereaved because 'physical illness under treatment' was significantly associated with morbidity. However, this persistent prevalence might suggest prolonged bereavement distress because dissatisfaction with EOL (their caregiving and the physician's care) was strongly associated with potential psychiatric disorders in this study.

Among the characteristics of patients/bereaved, 'bereaved spouse's history of psychiatric disorders prior to the patient's death' was the most highly correlated factor (OR = 3.19) and replicated previous studies on the indicators of vulnerability to bereavement stress [5,9,17]. Patients with stomach cancer in this study might have a higher rate of psychological symptoms because the highest rate of mixed anxiety/depression symptoms (20%) was seen with stomach cancer patients among 22 cancer types in a large cohort study [26]. Considering the positive association between patient and caregiver psychological distress in meta-analyses [27,28], patients' psychological distress factors of 'stomach cancer' or 'usage of psychiatric consultation service' could raise spouses' psychological distress prior to the patient's death. In addition, because psychological distress of caregivers prior to the patient's death predicted its prevalence after bereavement in a longitudinal multisite study [16], the initial detection of spouses with high psychological distress prior to the patient's death might be the most useful strategy for preventing subsequent impaired mental health among the bereaved.

**Table 3.** Factors associated with potential psychiatric disorders among bereaved spouses of cancer patients: univariate analysis

Variables	Potential psychiatric disorders						Analysis	
	Total		Presence		Absence		$\chi^2$	p
	n	(%)	n	(%)	n	(%)		
Deceased patients' characteristics								
Age (< 65 years)	386	(47.0)	198	(51.3)	188	(48.7)	4.56	0.04
Time since cancer diagnosis to death (< 1 year)	285	(34.7)	144	(50.5)	141	(49.5)	1.69	0.20
Duration of last hospital admission (< 1 week)	182	(22.2)	93	(51.1)	89	(48.9)	1.25	0.27
Place of death (Palliative care unit)	402	(49.0)	190	(47.3)	212	(52.7)	0.02	0.94
History of usage of psychiatric consultation service	152	(18.5)	87	(57.2)	65	(42.8)	7.24	<0.01
Cancer site								
Lung	241	(29.4)	113	(46.9)	128	(53.1)	0.05	0.88
Pancreas	88	(10.7)	39	(44.3)	49	(55.7)	0.40	0.57
Stomach	60	(7.3)	38	(63.3)	22	(36.7)	6.56	0.02
Colon	63	(7.7)	24	(38.1)	39	(61.9)	2.42	0.15
Head and neck	60	(7.3)	25	(41.7)	35	(58.3)	0.89	0.42
Esophagus	45	(5.5)	26	(57.8)	19	(42.2)	2.03	0.17
Breast	41	(5.0)	20	(48.8)	21	(51.2)	0.03	0.87
Liver	38	(4.6)	17	(44.7)	21	(55.3)	0.12	0.74
Biliary tract	33	(4.0)	19	(57.6)	14	(42.4)	1.41	0.29
Lymphoma	9	(1.1)	4	(44.4)	5	(55.6)	0.03	1.00
Bereaved spouses' characteristics								
Age (< 65 years)	307	(37.4)	171	(55.7)	136	(44.3)	13.94	<0.01
Gender (Male)	220	(26.8)	98	(44.5)	122	(55.5)	1.08	0.34
Time since bereavement (< 3 years)	322	(39.2)	175	(54.3)	147	(45.7)	10.55	<0.01
Living status (Living alone)	363	(44.2)	171	(47.1)	192	(52.9)	0.04	0.88
Employment status (Employed)	216	(26.3)	106	(49.1)	110	(50.9)	0.30	0.63
Education ( $\leq 9$ years)	121	(14.7)	51	(42.1)	70	(57.9)	1.65	0.23
Physical illness under treatment	424	(51.6)	227	(53.5)	197	(46.5)	14.10	<0.01
History of any psychiatric disorder prior to patients' death	60	(7.3)	43	(71.7)	17	(28.3)	15.37	<0.01
Bereavement experience after the death of spouse	196	(23.9)	91	(46.4)	105	(53.6)	0.12	0.74
Religiousness	311	(37.9)	157	(50.5)	154	(49.5)	1.89	0.18
Involvement in end-of-life caregiving (Everyday)	579	(70.5)	285	(49.2)	294	(50.8)	2.94	0.09
Dissatisfaction with end-of-life caregiving								
Knowledge of physical symptoms and management	235	(28.6)	130	(55.3)	105	(44.7)	9.01	<0.01
Professional supports for physical symptoms and management	177	(21.6)	104	(58.8)	73	(41.2)	12.31	<0.01
Knowledge of psychological symptoms and management	228	(27.8)	119	(52.2)	109	(47.8)	3.20	0.08
Professional supports for psychological symptoms and management	208	(25.3)	122	(58.7)	86	(41.3)	14.99	<0.01
Time spent communicating with patients	169	(20.6)	99	(58.6)	70	(41.4)	10.93	<0.01
Dissatisfaction with physicians' end-of-life care								
Treatment of physical symptoms	67	(8.2)	49	(73.1)	18	(26.9)	19.44	<0.01
Treatment of psychological symptoms	119	(14.5)	71	(59.7)	48	(40.3)	8.66	<0.01
Time spent communicating with patients	191	(23.3)	104	(54.5)	87	(45.5)	5.21	<0.01
Time spent communicating with patients' families	232	(28.3)	123	(53.0)	109	(47.0)	4.17	0.05

Fisher's exact test was performed when the sample number was less than 10. All variables were coded as: 0 = absence, 1 = presence.

**Table 4.** Factors associated with potential psychiatric disorders among bereaved spouses of cancer patients: multivariate logistic regression analysis

Variables	Beta	SE	OR	95% CI	p
Deceased patients' characteristics					
History of usage of psychiatric consultation service	0.42	0.20	1.52	1.02–2.26	0.04
Stomach cancer	0.63	0.30	1.87	1.04–3.38	0.04
Bereaved spouses' characteristics					
Age (< 65 years)	0.72	0.17	2.06	1.47–2.88	<0.01
Time since bereavement (< 3 years)	0.46	0.16	1.58	1.15–2.17	<0.01
Physical illness under treatment	0.82	0.17	2.26	1.62–3.16	<0.01
History of any psychiatric disorder prior to the patient's death	1.16	0.33	3.19	1.68–6.06	<0.01
Dissatisfaction with end-of-life caregiving					
Knowledge of physical symptoms and management	0.32	0.18	1.38	0.97–1.96	0.07
Time spent communicating with patients	0.44	0.20	1.55	1.05–2.30	0.03
Dissatisfaction with physicians' end-of-life care					
Treatment of physical symptoms	1.24	0.31	3.44	1.89–6.26	<0.01

Beta values indicate standardized regression coefficients on the final model after backward elimination. All variables were coded as: 0 = absence, 1 = presence. SE, standard error; OR, odds ratio; CI, confidence interval.

For the dissatisfaction with EOL care, 'dissatisfaction with physician's treatment of physical symptoms' was the most highly associated with potential psychiatric disorders (OR = 3.44). Unrelieved pain of female cancer patients during their last months of life showed a positive association with psychological morbidity such as sleep disorders in the widowers 4–5 years after bereavement [29]. Additionally, EOL care discussions are associated with less aggressive medical care, such as ventilation and resuscitation and less major depressive disorders in bereaved caregivers [15]. Therefore, satisfactory discussions about physical treatment in EOL care are helpful not only for the patients but also for the caregivers' psychological adjustment. Another factor, 'dissatisfaction with time spent communicating with patients' was significantly associated (OR = 1.55). A recent systematic review of communication with terminally ill patients and their families [30] indicated a lack of quantitative study. Communication skills training for healthcare professionals to improve discussions between patients and caregivers about EOL issues fostering realistic forms of hope is an essential future task for preventive intervention of spousal morbidity after bereavement [30].

We derived several implications for practice and research. In practice, we could obtain the following several indicators for early detection of high-risk spouses prior to the patient's death: 'patients using psychiatric consultation service', 'patients with stomach cancer', 'bereaved with a history of psychiatric disorder', 'dissatisfaction with time spent communicating with patients', and 'dissatisfaction with physician's treatment of physical symptoms'. Along with the early detection of spouses with these risk factors, nurse-assisted [31] or pharmacist-assisted [32] psychiatric referral programs using the 'Distress and Impact Thermometer' might be useful for directly evaluating psychological distress among spouses in EOL practice. In research, we could obtain the following possible strategies for preventive intervention of spousal morbidity after bereavement: assistance for improving 'discussions with physicians about physical treatment in EOL care' and 'discussions between patients and caregivers about EOL issues' would be effective. Development of communication skills training for healthcare professionals to improve these discussions must be considered in future research.

For the study limitations, first, the lack of an exact response rate was a critical methodological limitation. Nevertheless, we believe our estimated sample rate (31%) was adequate because the population of bereaved spouses included those who had died after the patient's

death. Second, two sample biases might exist. One was caused by the data collection site, a single cancer center in Japan. However, we do not believe that this institutional bias had a serious effect on the representation of Japanese bereaved spouses of cancer patients because 90% of cancer patients in Japan die in a hospital [19]. In addition, the bereaved with high impaired mental health might have been more motivated to take part in the study. This might have resulted in an inflated number of potential psychiatric disorders. Third, this was a cross-sectional study, and we could not discuss the time course of the prevalence or any causality between impaired mental health and associated factors. In addition, it remains possible that there was a recall bias in answering the question about dissatisfaction with EOL care because it was such a long period for a retrospective report by the bereaved who had lost their partner several years earlier. Fourth, other important factors were not investigated in this study, such as the bereaved spouse's 'style of attachment to the deceased', 'function level among family members', 'perception of the dying process and whether this was traumatic', and 'available social support'. Finally, we have no objective data on EOL care; individuals whose spouses died 7 years ago would likely have had a very different experience in the oncology care setting compared with those whose spouses died more recently.

## Conclusions

Nearly half the bereaved spouses showed potential psychiatric disorders even 7 years after bereavement. Patients' psychological distress, bereaved spouses' history of psychiatric disorder, and dissatisfaction with EOL care were indicators of high-risk spouses.

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## Conflicts of interest

All authors declare that the answers to the questions on your competing interest form are all 'No' and therefore have nothing to declare.

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## Strontium-89 (Sr-89) chloride in the treatment of various cancer patients with multiple bone metastases

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### Abstract

**Background** Although the use of Sr-89 chloride in the treatment of patients with prostate and breast cancer has been widely reported, little information is available about its use for other malignancies. Here, we retrospectively analyzed the clinical profile of Sr-89 chloride in various patients with painful bone metastases.

**Methods** Entry criteria were a pathologically proven malignancy, clinically diagnosed multiple bone metastases, and adequate organ function. Sr-89 chloride (Metastron) was given by single intravenous infusion at 2 MBq/kg over 2 min. Self-reported outcome measures were used as a response index, including pain diary data on a 0–10 numeric rating scale (NRS).

**Results** Fifty-four consecutive patients with painful bone metastases were treated with Sr-89 chloride at the National Cancer Center Hospital East between March 2009 and July 2011, consisting of 26 with breast/prostate cancer and 28

with other malignancies (lung 8, head and neck 6, colorectal 6, others 8). Thirteen (24 %) patients experienced a transient increase in pain, which was categorized as a flare-up response. Grade 3–4 anemia was observed in 6 patients, 3 of whom required blood transfusion. Regarding efficacy, response rates and complete response rates were 71.2 % and 34.6 %, respectively, and time to response from the initiation of treatment was 36 days (range, 13–217). No significant difference in response rates was seen between patients with breast/prostate cancer and other cancers (breast/prostate 69.2 %, other 73.1 %;  $p = 0.76$ ).

**Conclusions** As in patients with breast and prostate cancer, Sr-89 chloride is a promising agent for the treatment of painful bone metastases in patients with various other malignancies.

**Keywords** Palliative care · Radiation oncology · Radiation therapy · Radionuclide · Pain control

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### Background

The prevalence of painful osseous metastases varies among different types of cancer. Approximately 65 % of patients with prostate or breast cancer and 35 % of those with advanced cancers of the lung, thyroid, and kidney develop symptomatic skeletal metastases. The management of bone pain in these patients remains challenging, and no standardized procedures have yet been adopted. In patients with multifocal osteoblastic metastases, systemic administration of radiopharmaceuticals is the preferred adjunctive therapy for pain palliation.

Similar to calcium, strontium is a divalent cation that is incorporated into hydroxyapatite in bone after intravenous injection [1]. Sr-89 chloride (Metastron) is the first U.S.

Food and Drug Administration-approved radiopharmaceutical for bone pain palliation. The therapeutic effect derives from the beta particles, which have an energy penetration range of up to 6–7 mm in soft tissues and 3–4 mm in bone [2]. Sr-89 has a half-life of 50.5 days, and decays to stable yttrium-89, emitting high-energy beta particles ( $E_{\max}$ , 1.46 MeV) and 0.01 % of gamma-rays (910 keV). Administration poses no radiation risk to others, and patients can accordingly be treated on an outpatient basis. Studies of Sr-89 pharmacokinetics have demonstrated that plasma clearance is variable (1.6–11.6 l/day), with overall total-body retention of 20 % in a healthy population at 90 days after injection, particularly in the normal skeleton. Osteoblastic lesions show as much as five times greater radiopharmaceutical uptake and more prolonged retention than areas of normal bone in the same patient (lesion/normal bone ratio, 5:1) [3, 4].

Although the clinical profile of Sr-89 for prostate or breast cancer patients has been widely described [3, 5–9], little information is available concerning patients with other malignant diseases. Here, we conducted a retrospective analysis to clarify the clinical profile of Sr-89 in patients with multiple bone metastases arising from various other cancers.

## Patients and methods

### Patients

Entry criteria were a pathologically proven malignancy, clinical presence of multiple bone metastases detected by bone scintigraphy, and adequate organ function.

Patients eligible for external-beam radiotherapy (RT) or surgery were basically excluded from Sr-89 candidates.

Written informed consent for treatment was obtained from all patients before the initiation of treatment. This study was approved by the Institutional Review Board of National Cancer Center Hospital, Japan.

### Pretreatment evaluation

All patients underwent a complete blood count and serum chemistry testing at entry. Patients who fulfilled any of the following criteria were ineligible: (1) white blood cell count less than  $2,000/\text{mm}^3$ ; (2) platelet count less than  $75,000/\text{mm}^3$ ; (3) hemoglobin less than 9 g/dl; and (4) serum creatinine greater than 2.0 mg/dl or creatinine clearance less than 30 ml/min. All patients underwent bone scintigraphy before treatment. Information about pain and analgesic effect was obtained by physician interview in accordance with standard NRS practice.

### Protocol treatment

Sr-89 chloride (Metastron) was given by single intravenous infusion at 2 MBq/kg over 2 min followed by a 20-ml saline flush. Premedication was not routinely performed.

### Follow-up, response evaluation, and toxicity

Patients visited the outpatient clinic for a complete blood test and interview every 2 weeks from the initiation of treatment until 2 months after treatment. Self-reported outcome measures were used as response index, including pain diary data on a 0–10 numeric rating scale (NRS) [10, 11]. Complete response (CR) was defined as a minimum NRS of 10 % or less than that at the initiation of treatment, partial response (PR) as a minimum of 50 % or less than that at the initiation of treatment, and no response (NR) as a minimum NRS of equal to or greater than that at the initiation of treatment.

Toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Biweekly follow-up was continued until toxicities were easily manageable.

### Statistical analysis

Survival curves were estimated using the Kaplan–Meier product-limits method with the log-rank test. Overall survival was calculated from the start of treatment to the date of death or last confirmed date of survival. Survival time was censored at the last confirmation date if the patient was alive. Univariate analysis was conducted using the log-rank test.

## Results

### Patient characteristics

Fifty-four consecutive patients with painful bone metastases were treated with Sr-89 chloride at the National Cancer Center Hospital East between March 2009 and July 2011. All patients were reviewed. Patient characteristics are listed in Table 1. Twenty-six patients (48 %) had breast or prostate cancer. Twenty-six (48 %) had received chemotherapy in the 6 months before the initiation of treatment, among whom the median interval between the last chemotherapy and protocol treatment was 87 days (range, 0–164). Thirty-one patients had received prior palliative radiotherapy for bone metastases.

Of the patients, 23 (43 %) had received bisphosphonate therapy before Sr-89 administration, and all these patients