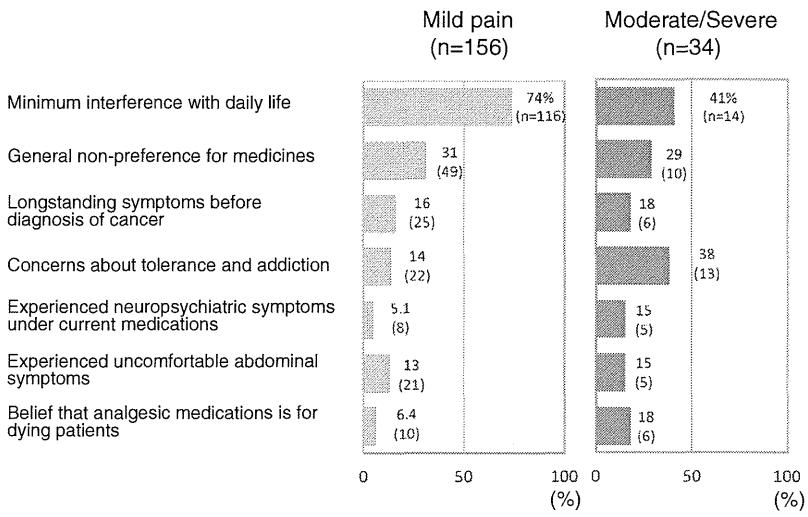


**Fig. 2** Reasons for not wanting pain treatment

regionwide palliative care outcomes, but the target patients receiving the greatest benefits from this program are those of a more advanced stage, not outpatients. This interpretation is supported by the findings that improvement occurred more clearly on considering the place of death and family-reported quality of life and quality of care in near-death patients [25]. The findings of this study that opioid consumption increased and the pain relief of terminally ill cancer patients reported by bereaved families improved also support this interpretation, that the intervention was actually directed to inpatients and patients at home.

The second potential interpretation is that intervention itself is weak for alleviating pain of outpatients. This interpretation is consistent with previous region-based intervention studies that failed to demonstrate clinically significant effects of the interventions [17, 18]. Outpatients have less frequent contact with medical professionals, and different strategies to improve pain may be necessary for outpatients and inpatients (e.g., for outpatients, intervention to increase regular contact such as telephone monitoring) [12, 16].

The third potential interpretation is that the severity of pain in this study population is not so high, and this could make interventions less effective due to ceiling effects. The prevalence of pain observed in this study is generally consistent with previous studies [1, 5–11]. Previous studies on cancer outpatients reported a pain prevalence of 60–70 %, and moderate/severe pain of 20–30 % [1, 5–11]. For instance, in an Ontario cohort, 53 % of ambulatory cancer patients reported some levels of pain, and 22 % reported moderate/severe pain [7]. The corresponding figures in this study are 57 and 16 %, respectively. Although direct comparisons of pain prevalence are difficult due to differences in study populations, settings, healthcare systems, and the survey methodology, the patients recruited and sampled in this study seems to be similar to those of previous studies; also, the pain intensity of patients with a lower performance status showed no significant changes. Future studies designed to include more patients with moderate or severe pain might lead to different results.

The fourth possible interpretation is the complex nature of pain as an outcome. Many studies reported that cancer patients do not simply want relief from pain, but they actually struggle to achieve an acceptable balance between interference with daily life from pain and other troublesome experiences (e.g., somnolence from pain medications) or psychological issues [16, 32, 33]. In this study, patients listed a variety of factors as the reasons they do not want pain treatment, such as minimum interference with daily life, general nonpreference for medicines, longstanding symptoms before diagnosis of cancer, concerns about tolerance and addiction, and experienced troublesome symptoms under current medications. In addition, this study revealed that the patient-reported quality of life was an independent determinant of needs for further pain treatment independent of the pain intensity itself. That is, patients do or do not want pain treatment in consideration of not only the pain intensity itself but also many aspects of the quality of life (e.g., functional status and other symptoms such

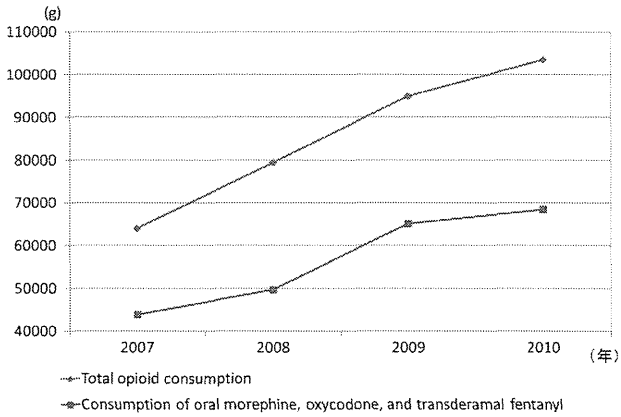


**Fig. 3** Changes in opioid consumption

as somnolence and abdominal symptoms) as well as their values (e.g., general nonpreference for medicines). Increased opioid consumption at a regional level did not lead to a decrease in pain intensity in outpatients. These observations further highlight the complex nature of pain treatment. Some patients were willing to accept mild to moderate pain as this had minimum interference on daily life, and they did not prefer medicines in general. Some patients had experienced neuropsychiatric symptoms under the current medications and were rather willing to accept moderate levels of pain. As a clinical implication, patient-tailored intervention is the only established way to optimize pain treatment for cancer patients [12, 13]. As research implication, while pain intensity and opioid consumption may be "too easy" estimates to evaluate the quality of pain management, a novel indicator to integrate the trade-off nature of pain experience and degree of respecting patient values would be necessary for future research in palliative care fields [1, 2, 37, 38].

Despite the strength of this study regarding the success in obtaining nearly representative data at a regional level, this study has several limitations. First, we obtained only the pain intensity because pain was not a primary end-point, and other measurements, such as satisfaction, pain relief, and quality indicator (e.g., pain management index), were not obtained. Second, a lack of data from medical records makes it difficult to determine whether a patient has received adequate pain management or the involvement of specialized palliative care services. Third, due to the lack of a control group, we cannot conclude that the changes observed in this study are a result of the interventions or national trends. Fourth, the outcomes measured with questionnaire surveys might have been affected by selection and response bias. Fifth, the data might not be a fully representative regional sample, although 80 % of hospital beds were included. Sixth, data reported by bereaved families may be affected by recall bias and the proxy nature.

In conclusion, despite the many improvements observed, this comprehensive regional palliative care program failed to demonstrate improvement in pain intensity in cancer outpatients. The potential interpretations are that outpatients are less likely to be regarded as the main target population in such a program; intervention itself is weak (too global), and the study population experienced generally well-controlled pain. To improve the pain experience of cancer outpatients, an intensive, patient-tailored intervention seems to be more promising than region-based intervention. The single use of pain intensity or opioid consumption as an outcome may be inappropriate to understand the overall experience of patients.

**Conflict of interest** This study was funded by the Third Term Comprehensive Control Research for Cancer Health and Labor Sciences Research Grants in Japan. The authors have no conflicts of interest.

## References

1. van den Beuken-van E, de Rijke JM, Kessels AG et al (2007) Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol 18:1437–1449
2. Deandrea S, Montanari M, Moja L et al (2008) Prevalence of undertreatment in cancer pain. A review of published literature. Ann Oncol 19:1985–1991
3. Apolone G, Corli O, Caraceni A et al (2009) Pattern and quality of care of cancer pain management. Results from the Cancer Pain Outcome Research Study Group. Br J Cancer 100:1566–1574
4. Shin DW, Hwang SS, Oh J et al (2012) Variations in pain management outcomes among palliative care centers and the impact of organizational factors. Cancer 118:5688–5697
5. Seow H, Barbera L, Sutradhar R et al (2011) Trajectory of performance status and symptom scores for patients with cancer during the last six months of life. J Clin Oncol 29:1151–1158
6. Cleeland CS, Gonin R, Hatfield AK et al (1994) Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 330:592–596
7. Barbera L, Seow H, Howell D et al (2010) Symptom burden and performance status in a population-based cohort of ambulatory cancer patients. Cancer 116:5767–5776
8. Barbera L, Seow H, Husain A et al (2012) Opioid prescription after pain assessment: a population-based cohort of elderly patients with cancer. J Clin Oncol 30:1095–1099
9. Yamagishi A, Morita T, Miyashita M et al (2009) Symptom prevalence and longitudinal follow-up in cancer outpatients receiving chemotherapy. J Pain Symptom Manag 37:823–830
10. Valeberg BT, Rustoen T, Bjordal K et al (2008) Self-reported prevalence, etiology, and characteristics of pain in oncology outpatients. Eur J Pain 12:582–590
11. Schuit KW, Sleijfer DT, Meijler WJ et al (1998) Symptoms and functional status of patients with disseminated cancer visiting outpatient departments. J Pain Symptom Manag 16:290–297
12. Bennett MI, Bagnall AM, Jose CS (2009) How effective are patient-based educational interventions in the management of cancer pain? Systematic review and meta-analysis. Pain 143:192–199
13. Goldberg GR, Morrison RS (2007) Pain management in hospitalized cancer patients: a systematic review. J Clin Oncol 25:1792–1801
14. Herman AD, Johnson TM 2nd, Ritchie CS et al (2009) Pain management interventions in the nursing home: a structured review of the literature. J Am Geriatr Soc 57:1258–1267
15. Lorenz KA, Krebs EE, Bentley TG et al (2009) Exploring alternative approaches to routine outpatient pain screening. Pain Med 10:1291–1299
16. Luckett T, Davidson PM, Green A, et al. Assessment and management of adult cancer pain: a systematic review and synthesis of recent qualitative studies aimed at developing insights for managing barriers and optimizing facilitators within a comprehensive framework of patient care. J Pain Symptom Manage, in press.
17. Elliott TE, Murray DM, Oken MM et al (1997) Improving cancer pain management in communities: main results from a randomized controlled trial. J Pain Symptom Manag 13:191–203
18. Hoffmann W, Munzinger H, Horstkotte E et al (2004) A population-based evaluation of an intervention to improve advanced stage cancer pain management. J Pain Symptom Manag 28:342–350
19. Bruera E, Neumann CM, Gagnon B et al (1999) Edmonton Regional Palliative Care Program: impact on patterns of terminal cancer care. CMAJ 161:290–293
20. Gómez-Batiste X, Caja C, Espinosa J et al (2012) The Catalonia World Health Organization demonstration project for palliative care implementation: quantitative and qualitative results at 20 years. J Pain Symptom Manag 43:783–794
21. Gilbert JE, Howell D, King S et al (2012) Quality improvement in cancer symptom assessment and control: the Provincial Palliative

Care Integration Project (PPCIP). J Pain Symptom Manag 43:663–678
22. Dudgeon DJ, Knott C, Chapman C et al (2009) Development, implementation, and process evaluation of a regional palliative care quality improvement project. J Pain Symptom Manag 38:483–495
23. Jordhøy MS, Fayers P, Saltnes T et al (2000) A palliative-care intervention and death at home: a cluster randomized trial. Lancet 356:888–893
24. Jordhøy MS, Fayers P, Loge JH et al (2001) Quality of life in palliative cancer care: results from a cluster randomized trial. J Clin Oncol 19:3884–3894
25. Morita T, Miyashita M, Yamagishi A et al (2013) Effects of a programme of interventions on regional comprehensive palliative care for patients with cancer: a mixed-methods study. Lancet Oncol 14:638–646
26. Morita T, Miyashita M, Yamagishi A et al (2012) A region-based palliative care intervention trial using the mixed-method approach: Japan OPTIM study. BMC Palliat Care 11:2
27. Imura C, Morita T, Kato M et al (2013) How and why did a regional palliative care program lead to changes in a region? A qualitative analysis of the Japan OPTIM-study. J Pain Symptom Manag. doi:10.1016/j.jpainsymman.2013.06.002
28. Morita T, Sato K, Miyashita M, et al. 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. Support Care Cancer, in press
29. Uki J, Mendoza T, Cleeland CS et al (1998) A brief cancer pain assessment tool in Japanese: the utility of the Japanese Brief Pain Inventory—BPI-J. J Pain Symptom Manag 16:364–373
30. Morita T, Hirai K, Sakaguchi Y et al (2004) Measuring the quality of structure and process in end-of-life care from the bereaved family perspective. J Pain Symptom Manag 27:492–501
31. Miyashita M, Morita T, Sato K et al (2008) Good Death Inventory: a measure for evaluating good death from the bereaved family member's perspective. J Pain Symptom Manag 35:486–498
32. Jacobsen R, Møldrup C, Christrup L et al (2009) Patient-related barriers to cancer pain management: a systematic exploratory review. Scand J Caring Sci 23:190–208
33. Weiss SC, Emanuel LL, Fairclough DL et al (2001) Understanding the experience of pain in terminally ill patients. Lancet 357:1311–1315
34. Jacobsen R, Sjøgren P, Møldrup C et al (2007) Physician-related barriers to cancer pain management with opioid analgesics: a systematic review. J Opioid Manag 3:207–214
35. Oldenmenger WH, Sillevis Smitt PA, van Dooren S et al (2009) A systematic review on barriers hindering adequate cancer pain management and interventions to reduce them: a critical appraisal. Eur J Cancer 45:1370–1380
36. Morita T, Miyashita M, Shibagaki M et al (2006) Knowledge and beliefs about end-of-life care and the effects of specialized palliative care: a population-based survey in Japan. J Pain Symptom Manag 31:306–316
37. Popovic M, Nguyen J, Chen E, Di Giovanni J, Zeng L, Chow E (2012) Comparison of the EORTC QLQ-BM22 and the FACT-BP for assessment of quality of life in cancer patients with bone metastases. Expert Rev Pharmacoecon Outcomes Res 12:213–219
38. Keirns CC, Goold SD (2009) Patient-centered care and preference-sensitive decision making. JAMA 302:1805–1806

JOURNAL OF PALLIATIVE MEDICINE
Volume 17, Number 6, 2014

DOI: 10.1089/jpm.2013.0613

# Predictive Factors for Nausea or Vomiting in Patients with Cancer Who Receive Oral Oxycodone for the First Time: Is Prophylactic Medication for Prevention of Opioid-Induced Nausea or Vomiting Necessary?

Yuko Kanbayashi, PhD[1,2] and Toyoshi Hosokawa, MD, PhD[2,3]

## Abstract

***Objectives:*** To identify predictive factors for nausea or vomiting in patients with cancer who receive oral opioid analgesics for the first time.

***Methods:*** The participants were 280 hospitalized patients with cancer who were given oral opioid analgesics for relief of cancer pain for the first time at our hospital between January 2008 and December 2011. According to previous studies, predictors evaluated were factors potentially affecting nausea or vomiting. For nausea, the following scoring for response was used: 0 = absence of nausea; 1 = presence of nausea for 3 days after the start of oral oxycodone but continued to take oxycodone; 2 = presence of nausea for 3 days and discontinued oxycodone due to nausea. For vomiting, at least 1 vomiting episode during the 3 days was regarded as vomiting-positive. Multivariate ordered logistic regression analysis was performed to identify the predictive factors for nausea or vomiting in cancer patients.

***Results:*** This analysis identified gender (male) (odds ratio [OR] = 0.429), lung cancer (OR = 2.049), and steroid use (OR = 0.417) were significant factors for the occurrence of opioid-induced nausea. For vomiting, gender (male) (OR = 0.4) and use of dopamine $D_2$ blockers (OR = 2.778) were significant factors.

***Conclusions:*** Female gender was found to be predictive factors for the occurrence of nausea. Lung cancer might be closely associated with opioid-induced nausea. The use of steroids might be effective as prophylaxis for nausea. Female gender was also a predictive factor for the occurrence of vomiting. Vomiting occurred even if dopamine $D_2$ blockers (prophylactic medication) were given.

## Introduction

NAUSEA OR VOMITING occurs frequently (10% to 40%) in patients receiving oral opioids, which may lead to the discontinuation of opioid use, thereby compromising pain management.[1–3] Opioids stimulate the medullary chemoreceptor trigger zone (CTZ), increase vestibular sensitivity, and have effects on the gastrointestinal tract. It has been common to prescribe antiemetic prophylaxis, such as dopamine type 2 ($D_2$) blockers, to decrease the incidence of nausea and vomiting in patients with cancer receiving oral opioid analgesics for the first time. However, we sometimes find that patients must discontinue opioid use due to nausea or vomiting, even with antiemetic prophylaxis. There has been little evidence indicating the efficacy of ant-emetic prophylaxis for opioid-induced nausea and vomiting.[4–8] Thus, a retrospective study was carried out to identify predictive factors for nausea or vomiting in patients with cancer who were given opioids for the first time, in order to be contributory to establish optimal treatment of cancer pain.

## Patients and Methods

### *Study term and participants*

Patient care records were searched to identify 280 hospitalized patients with cancer who were given oral opioid analgesics for relief of cancer pain for the first time at the University Hospital of Kyoto Prefectural University of Medicine between

Departments of [1]Hospital Pharmacy, [2]Pain Treatment and Palliative Care Unit, University Hospital, [3]Departments of Pain Management and Palliative Care Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan.
Accepted December 17, 2013.

January 2008 and December 2011. The exclusion criteria in the study protocol were having received cancer chemotherapy, radiation therapy or surgery within 2 weeks before or 1 week after administration of opioid analgesics and experiencing continuous nausea or vomiting due to organic or functional complications at the start of opioid administration. Patients with whom no communication was possible were excluded from participation. Oxycodone is currently most used as an opioid analgesic for moderate to severe cancer-related pain in Japan, so patients given oxycodone for the first time were included.[9]

This study was performed with the approval of the Ethics Review Boards of Kyoto Prefectural University of Medicine.

### *Statistical analysis*

**Extraction of variables.** According to previous studies,[1–8] the predictors evaluated were factors potentially affecting nausea or vomiting. They were demographic factors (gender, age), initial daily dose of oxycodone, concomitant medication (dopamine $D_2$ blockers, steroids, benzodiazepines, nonsteroidal anti-inflammatory drugs, histamine $H_2$-receptor antagonist, proton pump inhibitor, magnesium oxide, stimulant laxatives), and type of cancer (lung, digestive organ, liver, hematologic, breast, gynecologic, urologic, head and neck, and others). Concomitant medication including dopamine $D_2$ blockers (prophylactic medication) for at least 3 days after starting oral oxycodone was extracted. The incidence of opioid-induced nausea or vomiting that appeared within the 3 days after starting oral oxycodone was investigated from the medical records. The occurrence of nausea or vomiting was recorded by interviewing the patients in daily clinical practice by the treating physician and/or primary nurse. For nausea, the following scoring for response was used: 0 = absence of nausea; 1 = presence of nausea within 3 days but continued to take oxycodone; and 2 = presence of nausea within 3 days and oxycodone was discontinued due to nausea. For vomiting, at least 1 vomiting episode during the 3 days was regarded as vomiting-positive. As for predictors, binary scales were used for gender (female = 0; male = 1), and miscellaneous (no = 0; yes = 1).

**Statistical–analytical approach.** The actual procedure used was multivariate logistic regression analysis. For nausea, ordered logistic regression analysis was used because the severity of nausea was evaluated by a graded scale. Variables were screened by examining for multicollinearity (correlation coefficient $r > 0.7$), which occurs when correlations exist among the variables and results in the use of an inappropriate model. Univariate analysis between outcome and each of candidate independent variable was performed first. A

TABLE 1. PATIENT CHARACTERISTICS AND FACTORS THAT MAY POTENTIALLY IMPACT NAUSEA OR VOMITING ($N = 280$)

| | n *(%)* | Mean ± SD *(range)* | p *(nausea)* | p *(vomiting)* |
|---|---|---|---|---|
| ***Demographic factors*** | | | | |
| Gender (male) | 172 (61.4) | | 0.038[a] | 0.014[a] |
| Age, years | | 64.8 ± 12.9 (16–92) | 0.838 | 0.711 |
| Initial daily dose of oxycodone, mg | | 11.7 ± 4.2 (5–30) | 0.115 | 0.006[a] |
| ***Concomitant medication*** | | | | |
| Dopamine $D_2$ blockers | 224 (80) | | 0.817 | 0.426 |
| Prochlorperazine maleate | 212 (75.7) | | 0.904 | 0.706 |
| Metoclopramide | 12 (4.29) | | 0.020[a] | 0.309 |
| Steroids | 45 (16.1) | | 0.090 | 0.786 |
| Benzodiazepines | 122 (43.6) | | 0.590 | 0.385 |
| NSAIDs | 198 (70.7) | | 0.390 | 0.309 |
| $H_2$RAs | 68 (24.3) | | 0.698 | 0.422 |
| PPIs | 93 (33.2) | | 0.475 | 0.825 |
| Magnesium oxide | 189 (67.5) | | 0.704 | 0.633 |
| Stimulant laxatives | 52 (18.6) | | 0.283 | 0.007[a] |
| ***Type of cancer*** | | | | |
| Lung | 56 (20.0) | | 0.046[a] | 0.933 |
| Digestive organ | 69 (24.6) | | 0.015[a] | 0.228 |
| Gastric | 16 (5.7) | | 0.916 | 0.803 |
| Colon | 16 (5.7) | | 0.269 | 0.634 |
| Pancreas | 19 (6.8) | | 0.121 | 0.257 |
| Esophageal | 18 (6.4) | | 0.149 | 0.283 |
| Liver | 13 (4.6) | | 0.227 | 0.938 |
| Hematologic | 21 (7.5) | | 0.468 | 0.555 |
| Myeloma | 11 (3.9) | | 0.773 | 0.239 |
| Lymphoma | 10 (3.6) | | 0.464 | 0.675 |
| Breast | 9 (3.2) | | 0.272 | 0.518 |
| Gynecologic | 13 (4.6) | | 0.659 | 0.385 |
| Urologic | 24 (8.6) | | 0.190 | 0.141 |
| Head and neck | 52 (18.6) | | 0.700 | 0.485 |
| Others | 23 (8.2) | | | |

[a] $p < 0.05$.
Binary scales were female = 0 and male = 1 for gender, and absent = 0 and present = 1 for others.
NSAIDs, monsteroidal anti-inflammatory drugs; $H_2$RA, histamine $H_2$-receptor antagonist; PPI, proton pump inhibitor.

TABLE 2. CATEGORIZATION OF NAUSEA AND VOMITING ($N=280$)

| *Response* (Y) | *Number of patients* |
|---|---|
| $Y$=nausea | |
| 0 | 191 |
| 1 | 65 |
| 2 | 24 |
| $Y$=vomiting | |
| 0 | 239 |
| 1 | 41 |

For nausea, the following scoring for response was used: 0=absence of nausea; 1=presence of nausea within 3 days after start of oral oxycodone but oxycodone was continued; 2=presence of nausea within 3 days and oxycodone was discontinued due to nausea.

For vomiting, at least 1 vomiting episode during the 3 days was regarded as vomiting-positive (no=0; yes=1).

multivariate logistic regression model was constructed using forward stepwise selection among several candidate variables with a variable entry criterion of 0.25 and a variable retention criterion of 0.1 (JMP® version 10; SAS Institute, Cary, NC). All statistical analyses were performed at a two-sided significance level of 0.05.

## Results

Table 1 shows the clinical characteristics of the patients, various factors that could be related to the occurrence of opioid-induced nausea or vomiting and results of univariate analysis. Table 2 shows the categorization of nausea and vomiting. For nausea, gender, urologic cancer, digestive organ cancer, hepatocellular carcinoma, hematologic malignancy, lung cancer, initial daily dose of oxycodone, steroid use, age, and use of dopamine $D_2$ blockers were identified by forward selection. This was followed by multivariate ordered logistic regression analysis using these variables. This analysis identified gender (in male; odds ratio [OR]=0.429], lung cancer (OR=2.049), and use of steroid (OR=0.417) as significant factors for the occurrence of opioid-induced nausea. Use of dopamine $D_2$ blockers (prophylactic medication) to prevent opioid-induced nausea was not a significant factor. For vomiting, gender, urologic cancer, digestive organ cancer, proton pump inhibitor therapy, steroid use, and use of dopamine $D_2$ blockers were identified by forward selection. Multivariate logistic regression analysis identified gender (in male; OR=0.4) and use of dopamine $D_2$ blockers (OR=2.778) as significant factors. Accuracy means the ratio of patients whose expected value is equal to observed value (Table 3).

## Discussion

The multivariate logistic regression analysis used in this study demonstrated that gender, lung cancer, and steroid use were closely associated with the occurrence of opioid-induced nausea. Gender and use of dopamine $D_2$ blockers were closely associated with vomiting. The analysis showed that female gender was a predictive factor for the occurrence of opioid-induced nausea or vomiting. This finding is in agreement with the results of other studies.[10–12] Clinicians need to be alert to the greater risk of opioid-induced nausea or vomiting among women.

As far as we can tell from a literature search, this is the first study to identify close association between lung cancer and opioid-induced nausea. Patients with advanced lung cancer frequently develop metastases to bone and brain, which sometimes cause hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[13–15] Hypercalcemia should be anticipated in patients with bone metastases. Patients may experience nausea/vomiting as a consequence of hypercalcemia and so on or other electrolyte

TABLE 3. RESULTS OF LOGISTIC REGRESSION ANALYSIS FOR VARIABLES EXTRACTED BY FORWARD SELECTION ($N=280$)

| | | | | | | *CI of odds ratio* | |
|---|---|---|---|---|---|---|---|
| *Variable* | *EV* | *SE* | $\chi^2$ *value* | p | *Odds ratio* | *Lower 95%* | *Lower 95%* |
| $Y$=nausea (accuracy=193/280) | | | | | | | |
| ***Gender (male)*** | −0.847 | 0.284 | 8.92 | 0.0028[a] | 0.429 | 0.246 | 0.747 |
| Urologic | 0.642 | 0.474 | 1.84 | 0.1754 | 1.901 | 0.751 | 4.813 |
| Digestive organ | −0.726 | 0.377 | 3.71 | 0.054 | 0.484 | 0.231 | 1.013 |
| HCC | −1.092 | 0.802 | 1.85 | 0.1733 | 0.336 | 0.070 | 1.615 |
| Hematologic | −0.778 | 0.569 | 1.87 | 0.1718 | 0.459 | 0.150 | 1.402 |
| ***Lung*** | 0.717 | 0.362 | 3.93 | 0.0476[a] | 2.049 | 1.008 | 4.166 |
| Initial dose of oxycodone/day | 0.053 | 0.030 | 3.16 | 0.0756 | 1.055 | 0.995 | 1.119 |
| ***Steroids*** | −0.874 | 0.414 | 4.47 | 0.0345[a] | 0.417 | 0.185 | 0.938 |
| Age | 0.003 | 0.010 | 0.1 | 0.7538 | 1.003 | 0.983 | 1.024 |
| Dopamine $D_2$ blockers | −0.030 | 0.316 | 0.01 | 0.9239 | 0.970 | 0.522 | 1.802 |
| $Y$=vomiting (accuracy=240/280) | | | | | | | |
| ***Gender (male)*** | −0.917 | 0.358 | 6.56 | 0.0105[a] | 0.400 | 0.198 | 0.806 |
| Urologic | 0.892 | 0.549 | 2.63 | 0.1046 | 2.439 | 0.831 | 7.160 |
| Digestive organ | −0.539 | 0.457 | 1.39 | 0.2382 | 0.584 | 0.238 | 1.428 |
| PPI | −0.677 | 0.418 | 2.63 | 0.1049 | 0.508 | 0.224 | 1.152 |
| Steroids | −0.820 | 0.647 | 1.61 | 0.2051 | 0.441 | 0.124 | 1.566 |
| ***Dopamine $D_2$ blockers*** | 1.022 | 0.514 | 3.96 | 0.0466[a] | 2.778 | 1.015 | 7.604 |

[a]$p<0.05$.

EV, estimated value; SE, standard error; CI, confidence interval; HCC, hepatocellular carcinoma; PPI, proton pump inhibitor.

disturbances, such as hyponatremia, hypokalemia, or metabolic alkalosis, which occur secondary to paraneoplastic syndromes.[16–18] Brain metastasis also causes nausea. Patients with lung cancer may, therefore, tend to not respond well to antiemetic therapy. We intend to further investigate differences in responses to antiemetics in patients with different diseases.

Use of dopamine $D_2$ blockers (prophylactic medication) to prevent opioid-induced nausea was ineffective, and vomiting occurred even if dopamine $D_2$ blockers were prescribed. The present results showed that the use of steroids was effective as prophylaxis. A previous study clarified the effectiveness of steroids for prevention of opioid-induced nausea.[19,20] Treatment with steroids often results in increased appetite, reduced nausea and improved well-being in patients with advanced metastatic cancer.[21] It might also be better to use steroid as prophylactic medication for prevention of opioid-induced nausea for patients with risk factors. Previous studies suggested other types of antiemetic drugs such as mirtazapine, 5-$HT_3$ receptor blockers, and antihistaminic might be effective for prevention of opioid-induced nausea.[22–25] In our study, steroids were used not only to prevent opioid-induced nausea or vomiting, but also to improve well-being (betamethasone 1–4 mg/d). Further studies will be needed in this issue.

In conclusion, female gender was found to be predictive factors for the occurrence of nausea given oral opioid analgesics for relief of cancer pain for the first time. Lung cancer might be closely associated with opioid-induced nausea. The use of steroids might be effective as prophylaxis for nausea. Female gender was also a predictive factor for the occurrence of vomiting. Use of dopamine $D_2$ blockers (prophylactic medication) to prevent opioid-induced nausea was not a significant factor, and vomiting occurred even if dopamine $D_2$ blockers were given.

This study has several limitations. First, the retrospective nature of the investigation may have decreased the reliability of the data collected. Second, this study was performed at a single institute and involved a relatively small number of patients, so the results should be confirmed in a further multicenter study.

In conclusion, our study demonstrated that gender, lung cancer, and steroid use were closely associated with the occurrence of opioid-induced nausea. Gender and use of dopamine $D_2$ blockers were closely associated with vomiting. These findings should be considered preliminary and in need of further refinement and study. However, statistical identification of factors associated with opioid-induced nausea or vomiting should contribute to establish optimal treatment of cancer pain.

## Author Disclosure Statement

No competing financial interests exist.

## References


1. Wirz S, Wittmann M, Schenk M, Schroeck A, Schaefer N, Mueller M, Standop J, Kloecker N, Nadstawek J: Gastrointestinal symptoms under opioid therapy: A prospective comparison of oral sustained-release hydromorphone, transdermal fentanyl, and transdermal buprenorphine. Eur J Pain 2009;13:737–743.
2. Porreca F, Ossipov MH: Nausea and vomiting side effects with opioid analgesics during treatment of chronic pain: mechanisms, implications, and management options. Pain Med 2009;10:654–662.
3. Laugsand EA, Kaasa S, Klepstad P: Management of opioid-induced nausea and vomiting in cancer patients: Systematic review and evidence-based recommendations. Palliat Med 2011;25:442–453.
4. Ishihara M, Iihara H, Okayasu S, Yasuda K, Matsuura K, Suzui M, Itoh Y: Pharmaceutical interventions facilitate premedication and prevent opioid-induced constipation and emesis in cancer patients. Support Care Cancer 2010;18: 1531–1538.
5. Ishihara M, Ikesue H, Matsunaga H, Suemaru K, Kitaichi K, Suetsugu K, Oishi R, Sendo T, Araki H, Itoh Y; Japanese Study Group for the Relief of Opioid-induced Gastrointestinal Dysfunction: A multi-institutional study analyzing effect of prophylactic medication for prevention of opioid-induced gastrointestinal dysfunction. Clin J Pain 2012;28: 373–381.
6. Aparasu R, McCoy RA, Weber C, Mair D, Parasuraman TV: Opioid-induced emesis among hospitalized nonsurgical patients: Effect on pain and quality of life. J Pain Symptom Manage 1999;18:280–288.
7. Porreca F, Ossipov MH: Nausea and vomiting side effects with opioid analgesics during treatment of chronic pain: mechanisms, implications, and management options. Pain Med 2009;10:654–662.
8. Glare P, Miller J, Nikolova T, Tickoo R. Treating nausea and vomiting in palliative care: a review. Clin Interv Aging. 2011; 6:243–59.
9. Koizumi W, Toma H, Watanabe K, Katayama K, Kawahara M, Matsui K, Takiuchi H, Yoshino K, Araki N, Kodama K, Kimura H, Kono I, Hasegawa H, Hatanaka K, Hiraga K, Takeda F: Efficacy and tolerability of cancer pain management with controlled-release oxycodone tablets in opioid-naive cancer pain patients, starting with 5 mg tablets. Jpn J Clin Oncol 2004;34:608–614.
10. Cepeda MS, Farrar JT, Baumgarten M, Boston R, Carr DB, Strom BL: Side effects of opioids during short-term administration: Effect of age, gender, and race. Clin Pharmacol Ther 2003;74:102–112.
11. Zun LS, Downey LV, Gossman W, Rosenbaumdagger J, Sussman G: Gender differences in narcotic-induced emesis in the ED. Am J Emerg Med 2002;20:151–154.
12. Zacny JP, Drum M: Psychopharmacological effects of oxycodone in healthy volunteers: Roles of alcohol-drinking status and sex. Drug Alcohol Depend 2010;107:209–214.
13. Langer C, Hirsh V: Skeletal morbidity in lung cancer patients with bone metastases: Demonstrating the need for early diagnosis and treatment with bisphosphonates. Lung Cancer 2010;67:4–11.
14. Kawabe T, Phi JH, Yamamoto M, Kim DG, Barfod BE, Urakawa Y: Treatment of brain metastasis from lung cancer. Prog Neurol Surg 2012;25:148–155.
15. Vantyghem MC, Balavoine AS, Wémeau JL, Douillard C: Hyponatremia and antidiuresis syndrome. Ann Endocrinol (Paris) 2011;72:500–512.
16. Yeung SC, Habra MA, Thosani SN: Lung cancer-induced paraneoplastic syndromes. Curr Opin Pulm Med 2011;17: 260–268.
17. Pelosof LC, Gerber DE: Paraneoplastic syndromes: An approach to diagnosis and treatment. Mayo Clin Proc 2010; 85:838–854.
18. van Meerbeeck JP, Fennell DA, De Ruysscher DK: Small-cell lung cancer. Lancet 2011;378:1741–1755

19. Allen TK, Jones CA, Habib AS: Dexamethasone for the prophylaxis of postoperative nausea and vomiting associated with neuraxial morphine administration: A systematic review and meta-analysis. Anesth Analg 2012;114:813–822.
20. Song JW, Park EY, Lee JG, Park YS, Kang BC, Shim YH: The effect of combining dexamethasone with ondansetron for nausea and vomiting associated with fentanyl-based intravenous patient-controlled analgesia. Anaesthesia 2011; 66:263–267.
21. Lundström S, Fürst CJ, Friedrichsen M, Strang P: The existential impact of starting corticosteroid treatment as symptom control in advanced metastatic cancer. Palliat Med 2009;23:165–170.
22. Peixoto AJ, Celich MF, Zardo L, Peixoto Filho AJ: Ondansetron or droperidol for prophylaxis of nausea and vomiting after intrathecal morphine. Eur J Anaesthesiol 2006;23:670–675.
23. Lu CW, Jean WH, Wu CC, Shieh JS, Lin TY: Antiemetic efficacy of metoclopramide and diphenhydramine added to patient-controlled morphine analgesia: a randomised controlled trial. Eur J Anaesthesiol 2010;27:1052–1057.
24. Chang FL, Ho ST, Sheen MJ: Efficacy of mirtazapine in preventing intrathecal morphine-induced nausea and vomiting after orthopaedic surgery. Anaesthesia 2010;65:1206–1211.
25. George RB, Allen TK, Habib AS: Serotonin receptor antagonists for the prevention and treatment of pruritus, nausea, and vomiting in women undergoing cesarean delivery with intrathecal morphine: A systematic review and meta-analysis. Anesth Analg 2009;109:174–182.

Address correspondence to:
*Yuko Kanbayashi, PhD*
*Department of Hospital Pharmacy*
*Kyoto Prefectural University of Medicine*
*Kawaramachi Hirokoji*
*Kamigyo-ku, Kyoto 602-8566*
*Japan*

*E-mail:* ykokanba@koto.kpu-m.ac.jp

# Effects of a programme of interventions on regional comprehensive palliative care for patients with cancer: a mixed-methods study

*Tatsuya Morita, Mitsunori Miyashita, Akemi Yamagishi, Miki Akiyama, Nobuya Akizuki, Kei Hirai, Chizuru Imura, Masashi Kato, Yoshiyuki Kizawa, Yutaka Shirahige, Takuhiro Yamaguchi, Kenji Eguchi*

*Lancet Oncol* 2013; 14: 638–46
Published Online
May 9, 2013
http://dx.doi.org/10.1016/S1470-2045(13)70127-X

See Comment page 571

Department of Palliative and Supportive Care, Palliative Care Team, and Seirei Hospice (T Morita MD), and Hamamatsu Cancer Support Center (C Imura RN), Seirei Mikatahara General Hospital, Hamamatsu, Shizuoka, Japan; Division of Palliative Nursing, Health Sciences, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan (Prof M Miyashita PhD); Department of Preventive Medicine and Public Health, School of Medicine, Keio University, Shinjuku-ku, Tokyo, Japan (A Yamagishi PhD); Faculty of Environment and Information Studies, Keio University, Fujisawa, Kanagawa, Japan (M Akiyama PhD); Psycho-Oncology Division, Chiba Cancer Center, Chiba, Chiba, Japan (N Akizuki MD); Department of Complementary and Alternative Medicine, Graduate School of Medicine and Center for the Study of Communication-Design, Osaka University, Osaka, Japan (K Hirai PhD); Center for Cancer Control and Information Services, National Cancer Center, Chuo-ku, Tokyo, Japan (M Kato MD); Department of Palliative Medicine, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan (Y Kizawa MD); Shirahige Clinic, Nagasaki, Nagasaki, Japan (Y Shirahige MD); Division of Biostatistics, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan (Prof T Yamaguchi PhD); and Division of Medical Oncology,

## Summary

**Background** Improvement of palliative care is an important public health issue, but knowledge about how to deliver palliative care throughout a region remains inadequate. We used surveys and in-depth interviews to assess changes in the quality of palliative care after regional interventions and to gain insights for improvement of palliative care at a regional level.

**Methods** In this mixed-methods study, a comprehensive programme of interventions for regional palliative care for patients with cancer was implemented from April 1, 2008, to March 31, 2011 in Tsuruoka, Kashiwa, Hamamatsu, and Nagasaki in Japan. Interventions included education, specialist support, and networking. We surveyed patients, bereaved family members, physicians, and nurses before and after the interventions were introduced. We also did qualitative interviews with health-care professionals after the interventions were introduced. Primary endpoints were numbers of home deaths, coverage of specialist services, and patient-reported and family-reported qualities of care. This trial is registered with UMIN Clinical Trial Registry, Japan (UMIN000001274).

**Findings** 859 patients, 1110 bereaved family members, 911 physicians, and 2378 nurses provided analysable preintervention surveys; 857 patients, 1137 bereaved family members, 706 physicians, and 2236 nurses provided analysable postintervention surveys. Proportions of home deaths increased significantly, from 348 of 5147 (6·76%) before the intervention programme to 581 of 5546 (10·48%) after the intervention programme ($p<0·0001$). Furthermore, 194 of 221 (87·78%) family members of patients who died at home answered that these patients had wanted to die at home. The ratio of patients who received palliative care services to all patients who died of cancer increased significantly (from 0·31 to 0·50; $p<0·0001$). The patient-reported (effect size 0·14; adjusted $p=0·0027$) and family-reported (0·23; $p<0·0001$) qualities of care were significantly better after interventions than before interventions. Physician-reported and nurse-reported difficulties decreased significantly after the introduction of the interventions. Qualitative interviews showed improved communication and cooperation between health-care professionals because of greater opportunities for interactions at various levels.

**Interpretation** A regional programme of interventions could improve the quality of palliative care. Improvement of communication between health-care professionals is key to improvement of services.

**Funding** Third Term Comprehensive Control Research for Cancer Health and Labor Sciences Research Grants of the Ministry of Health, Labour and Welfare of Japan.

## Introduction

Improvement of palliative care is an important health-care issue worldwide.[1] Several systematic reviews have shown the benefits of palliative care to patients and families.[2,3] Palliative care should thus be provided consistently throughout an entire region, and several studies have explored the effects of programmes of interventions in regional palliative care on place of death (ie, home death *vs* death in hospital, nursing home, or other location), use of palliative care services, patient-reported and family-reported outcomes, and health-care costs.[4–9] For example, a cluster-randomised controlled trial has shown that regional palliative care interventions helped to increase family satisfaction and the proportion of deaths occurring at home. However, whether such increases show patients' preferences, and how such changes occur, were not explored.[4–9]

In the past 10 years or so, the UK has implemented the Gold Standards Framework, which stresses communication and coordination in the community through development of a palliative care registry and regular meetings.[10] The results of a review[10] suggested that the most important perceived benefit of the Gold Standards Framework is enabling of communication between health-care professionals in the community—a finding consistent with those from studies in Australia,[11] Canada,[12] and the Netherlands.[13] These studies provide important insights into the potential benefits of regional palliative care programmes. However, clinical implications are few because the interventions often required structural or

financial changes in the health-care system (and thus could not be applied when such changes were difficult or unfeasible), and multidimensional outcomes (especially patient-reported outcomes) were not measured or were explored in only some populations and provided few insights about the regional effects of the interventions. A mixed-methods approach has been proposed as a potentially useful strategy to examine the effects of complex interventions,[14,15] but, to the best of our knowledge, no large-scale mixed-methods studies of regional palliative care interventions have been done.

The Japanese medical system is characterised by free access, fully covered by national insurance, and has no system of primary-care physicians.[16,17] Patients can freely access all medical institutions, but the organisation of palliative care resources varies widely between regions. 7% of patients who die from cancer die at home, another 7% die in inpatient hospices or palliative care units, and the rest die in hospitals.[17] As in other countries, how to deliver palliative care throughout the region and how to increase the numbers of patients who die in their preferred location are important issues in Japan.

We did a mixed-methods study to assess changes in various outcomes in regional palliative care after the introduction of a programme of interventions and to explore how the changes occurred. Our ultimate purpose was to get insights into provision of high-quality palliative care at a regional level.

## Methods

### Study design and participants

The Japan Outreach Palliative Care Trial of Integrated Regional Model (OPTIM) study is a mixed-methods study of a regional palliative care intervention trial for patients with cancer[18,19] that was done in four regions of Japan—specifically, Tsuruoka (Yamagata Prefecture), Kashiwa (Chiba Prefecture), Hamamatsu (Shizuoka Prefecture), and Nagasaki (Nagasaki Prefecture). All cooperative hospitals, general practice clinics, district nurse services, and other health-care organisations in these regions participated into the study.

Methods have been previously described;[19] the rationale for the study design and each endpoint, psychometric properties, item examples of measurement instruments, interventions, sample size calculations, and details of statistical analyses are presented in an accessible short-form protocol. The ethical and scientific validity of this study was confirmed by the institutional review board of this study and the boards of all participating hospitals. Our study was done according to the ethical guidelines for Epidemiological Research by the Ministry of Health, Labor and Welfare, and written informed consent was not necessary.

We surveyed participants, then introduced interventions to improve palliative care, and then surveyed participants again. Because of the absence of a registry system to identify all potential participants, we identified all hospitals, general practice clinics, and district nurse services in each area with reference to lists from the Japan Hospital Association and local information. Research coordinators at each institution identified and approached potential participants.

The aims of the surveys were to explore the perceived changes in quality of care and quality of life (patients and bereaved families) and the changes in perceived difficulties and knowledge (survey of doctors and nurses). Participants were administered identical questionnaires before and after the implementation of the programme of interventions.

We sent questionnaires by mail to all patients, bereaved family members, physicians, and nurses who met the inclusion criteria. We intended to obtain a sample that was as representative of each region as possible. Eligible patients were adults with metastatic or recurrent cancer of the lung, oesophagus, stomach, colon, rectum, pancreas, liver, biliary system, kidney, prostate, bladder, breast, ovary, or uterus, who had been informed of their malignancy and made outpatient visits to the oncology or relevant specialty department.

We identified bereaved family members in hospitals and at all general practice clinics with experience of caring for terminally ill patients with cancer. Inclusion criteria for bereaved family members were having an adult family member with cancer who had died in a health-care institution or at home (one family member listed as the main caregiver on the medical record was selected for each patient) who had had a primary tumour of the lung, oesophagus, stomach, colon, rectum, pancreas, liver, biliary system, kidney, prostate, bladder, breast, ovary, or uterus; received medical treatment from the institution on 3 days or more; and been informed of the malignancy. Bereaved family members of patients who died from treatment-associated complications or comorbidities or who died in intensive-care units were also excluded.

Physicians and nurses were recruited from hospitals, general practice clinics, and district nurse services. Hospital physicians and nurses working in cancer-related specialties, a representative physician of general practice clinics, and all district nurses with 3 years or more of clinical experience (ie, who had completed residency training) were eligible for inclusion. Health-care workers were excluded if they had not treated any cancer patients during the previous year.

We obtained preintervention data for outcomes before or in the early stage of the intervention period and postintervention data for outcomes after or in the late stage of the intervention period. The intervention programme was implemented from April 1, 2008, to March 31, 2011; these dates were prospectively defined. We got information about the location of death of patients with cancer from the national government registry and the number of patients who receive specialised palliative care services from each service for each year from 2007 to 2010. We consecutively recruited patients who were receiving

**Teikyo University School of Medicine, Itabashi-ku, Tokyo, Japan** (Prof K Eguchi MD)

Correspondence to:
Dr Tatsuya Morita, Department of Palliative and Supportive Care, Palliative Care Team, and Seirei Hospice, Seirei Mikatahara General Hospital, 3453 Mikatahara-cho, Kita-ku, Hamamatsu, Shizuoka 433-8558, Japan
**tmorita@sis.seirei.or.jp**

For the **accessible short-form protocol** see http://gankanwa.umin.jp/optim_protocol.pdf

**Panel 1: Interventions to improve regional palliative care**

Interventions introduced comprised four components. To improve the knowledge and skills of palliative care providers, pocket-size manuals of palliative care (a book and videos) and 13 assessment instruments (12 educational pamphlets for patients and families for each symptom, such as pain, and one comprehensive assessment instrument) were disseminated via printed materials and a web site, and used in educational workshops. To increase the availability of specialised palliative care services for community patients, each region established a community palliative care team through optimisiation of resources; the team provided outreach educational visits for community institutions. To coordinate community palliative care resources, each region established a regional palliative care centre and held a multidisciplinary conference to develop collaborative relationships between health-care workers in the region. Use of patient-held records to maintain continuity of care and introduction of a discharge planning system was encouraged. To provide information about palliative care, hand-sized leaflets, note-sized leaflets, posters, and DVDs were disseminated. Public libraries provided a set of 100 books about palliative care, and workshops were held for the general public.

medical treatment for cancer in participating hospitals between March 1 and April 30, 2008 (preintervention), and between Nov 1 and Dec 31, 2010 (postintervention). We consecutively sampled bereaved families of patients who died between April 1, 2007, and March 31, 2008 (preintervention), and between April 1, 2010, and March 31, 2011 (postintervention), and questionnaires were sent in October, 2008 (preintervention), and October, 2011 (postintervention). Physicians and nurses were sampled in February, 2008 (preintervention), and January, 2011 (postintervention). Interviews with participating clinical staff were done from Jan 6, to March 31, 2011.

### Interventions

Interventions were designed on the basis of a literature review, preliminary surveys, and discussion among the researchers and with health-care professionals in the study regions to resolve the identified major barriers to region-based palliative care.[18,19]

Four types of interventions were implemented—ie, those to improve the knowledge of, and skills in, palliative care (eg, dissemination of manuals and assessment instruments, interactive workshops), increase the availability of specialised palliative care services (eg, establishment of a new community palliative care team, outreach educational visits), coordinate community palliative care resources (eg, regional palliative care centres, whole-region interdisciplinary conferences, patient-held records, discharge-planning systems), and provide appropriate information about palliative care to the general public, patients, and families (panel 1).

To deliver the intervention, each region identified a team of local leaders, including a physician, a nurse, and a medical social worker who had already been working as a clinical specialist in the region, that was responsible for implementation. These leaders received a 2 day workshop from the research team before the interventions. To monitor and help with implentation of interventions, meetings between local leaders and the research group were held 25 times throughout the study, and a certified community nurse visited each region and followed up by telephone and email consistently.

We designed interventions so that structural or financial changes would not be needed in the health-care system, and aimed to optimise health-care resources within a region. With reference to the UK Medical Research Council recommendation[15] about complex interventions, we closely monitored the intensity of interventions, described the narrative intervention process in detail, and investigated the levels of exposure to interventions in the postintervention survey.

### Procedures

Our study had four primary endpoints—namely, the proportion of patients with cancer who died at home, coverage of specialist services (ie, the ratio of patients who received specialised palliative care services to all patients who died of cancer), and patient-reported and family-reported qualities of palliative care on the care evaluation scale.[20,21] We obtained the proportion of patients who died at home from the national government registry. As reference data, the mean home-death rate of all patients with cancer in Japan was obtained. The number of patients who received specialised palliative care services was defined as the total number of patients listed by each specialised palliative care service. Duplicate counting was permitted (ie, if patients used more than one specialised palliative care service, they were counted each time). We used the total score of three subscales (physical care provided by physicians, physical care provided by nurses, and psychoexistential care, each of which had three items) of the care evaluation scale as a single scale. Each item was scored on a 6-point Likert-type scale (1=improvement is very necessary; 6=improvement is not necessary at all); high values suggest that patients perceive little need for improvement.

Secondary endpoints were care burden, length of hospital admission, quality of life, difficulty of delivering palliative care, and knowledge of palliative care. We measured care burden on the basis of the care burden section of the caregiving consequences inventory,[22] which comprises four items about physical, emotional, practical, and economic burden scored from 1 ("strongly disagree") to 7 ("strongly agree"); high values suggest a high perceived care burden. Bereaved family members reported the length of inpatient hospital admission of "2 weeks or longer" in the last month of life. Quality of life of patients, as judged by both patients and bereaved

families (as a proxy for terminally ill patients), was measured with the good death inventory.[23,24] Each item was scored from 1 ("strongly disagree") to 7 ("strongly agree"); high values suggest a high perceived quality of life. Additionally, we asked bereaved family members about whether they believed that patients had died in their preferred place.[23]

Physician-reported and nurse-reported difficulty of delivering palliative care were measured with the palliative care difficulty scale,[25] which consists of five subscales (communication in multidisciplinary teams, community coordination, expert support, alleviation of symptoms, and communication with patients and families) that assess the frequency of problems in daily practice with a Likert-type scale scored from 1 ("never") to 5 ("very much"); high values suggest a high perceived difficulty. We measured physician-reported and nurse-reported knowledge about palliative care with the palliative care knowledge test.[26] Responses were scored as correct or incorrect; high test scores suggest a high level of knowledge about palliative care.

### Qualitative assessment

In addition to the surveys, all health-care professionals who had roles in the implementation of the interventions underwent semistructured face-to-face interviews with two trained research nurses in the late stages of, or after, the interventions—specifically between Jan 6 and March 31, 2011. Questions focused on the perceived changes and experiences during the study and perceived reasons for the changes. All interviews were audiotaped, transcribed verbatim, and subjected to thematic analysis on the basis of the grounded theory tradition.[27,28] Two nurse researchers (distinct from the research nurses who did the interviews) used a consistent comparison method to independently code interviews for major themes. Coding frameworks and assignments were discussed under the supervision of an experienced palliative care specialist (TM). Discussions between researchers resulted in full agreement about the codes and themes that emerged.

### Statistical analysis

We used logistic regression to compare changes in home death rates and ratios of patients who received specialised palliative care services before and after the interventions. The significance of interventions was assessed by time interaction terms (ie, time trend). For comparison with the national reference data for home deaths, we did repeated measures analysis with robust variances (ie, a generalised estimating equation approach) to account for the longitudinal nature of the data. Scores on the care evaluation scale, caregiving consequences inventory, palliative care difficulty scale, and palliative care knowledge test before and after the interventions were compared with the Student's $t$-test. We calculated Hedges' $g$ to estimate effect size.[29] For duration of hospital admission, we used the $\chi^2$ test for trend. For interpretation, we deemed effect sizes of 0·2 small, 0·5 moderate, and 0·8 large.[30] We did regressional analyses for all primary endpoints to adjust for participants' background characteristics, such as age, sex, and region.

To adjust for difference in the proportions of places of death of the patients sampled, the weighted means of death location according to census data of four regions

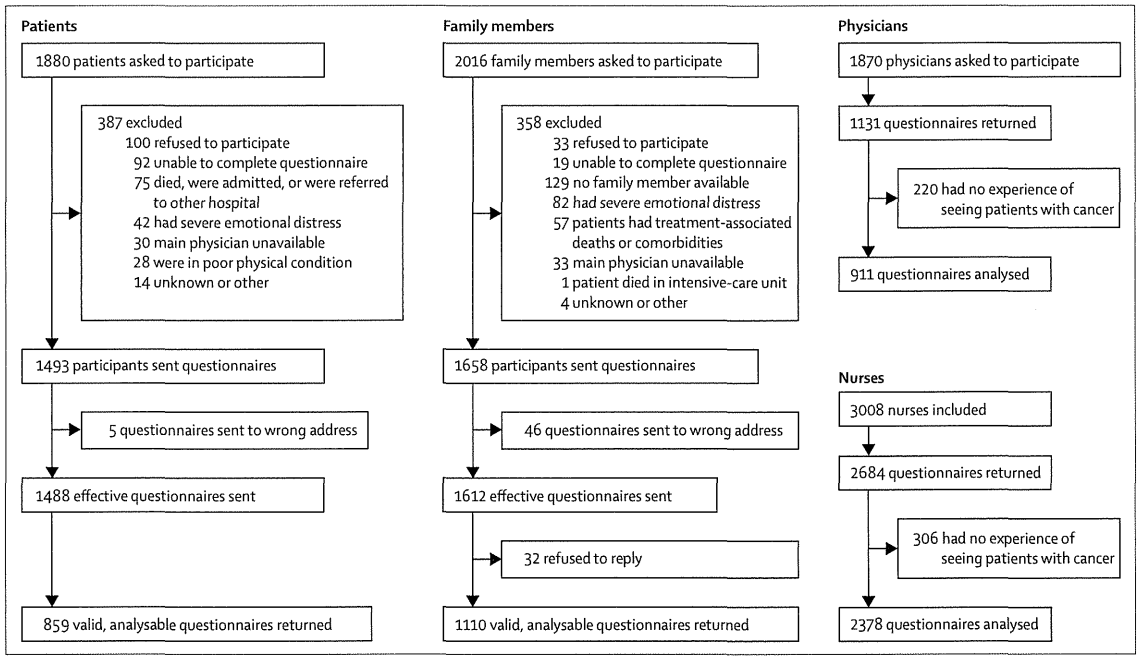


*Figure 1:* **Recruitment of patients, bereaved family members, physicians, and nurses before intervention programme**

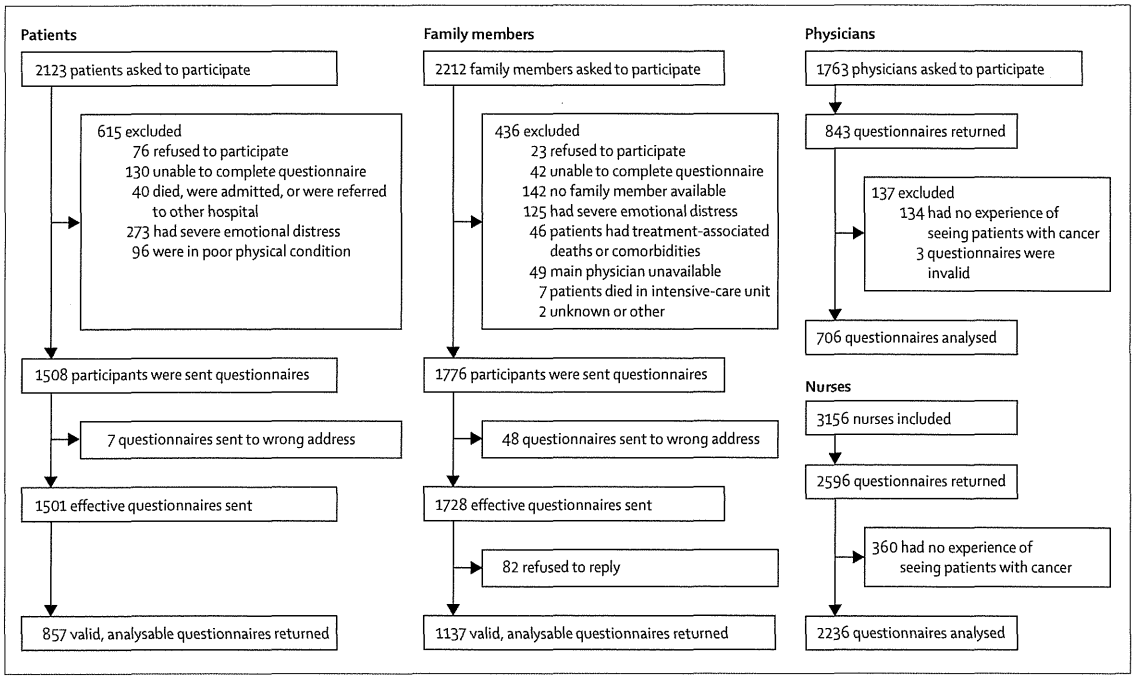


*Figure 2:* **Recruitment of patients, bereaved family members, physicians, and nurses after intervention programme**

| | n |
|---|---|
| **To improve knowledge of, and skills in, palliative care** | |
| Manuals disseminated | 24353 |
| Assessment instruments disseminated | 174891 |
| Participants of interactive workshops | 22189 |
| **To increase the availability of community-specialised palliative care services** | |
| Patients referred to a community palliative care team | 429 |
| Outreach educational visits | 38 |
| **To coordinate community palliative care resources** | |
| Consultations at regional palliative care centres | 6775 |
| Participants in whole-region interdisciplinary conferences | 5902 |
| Patient-held records disseminated | 13574 |
| Hospitals introducing a discharge-planning system | 23* |
| **To provide appropriate information about palliative care** | |
| Leaflets, posters, and DVDs disseminated | 202340 |
| Participants in public workshops | 10226 |

Data are n, and are from four study regions (Hamamatsu, Kashiwa, Nagasaki, and Tsuruoka) between April 1, 2008, and March 31, 2011. *Of 27 hospitals.

*Table 1:* **Number of interventions delivered to improve palliative care**

See Online for appendix

were used for bereaved family outcomes. We did not calculate inter-reliability statistics for the results of qualitative interviews with health-care professionals. We calculated sample sizes for four primary endpoints. We used SAS (version 9.3) for all analyses. We deemed two-sided p values of 0·0125 or less to be significant (we used the Bonferroni correction for multiple comparisons). This trial is registered with UMIN Clinical Trial Registry, Japan (UMIN000001274).


## Role of the funding source

The funding source had no role in study design; data collection, analysis, or interpretation; or the writing of the report. The corresponding author had full access to all data and final responsibility for the decision to submit for publication.


## Results

859 patients, 1110 bereaved family members, 911 physicians, and 2378 nurses were analysed in the preintervention survey, and 857 patients, 1137 bereaved family members, 706 physicians, and 2236 nurses in the postintervention survey (figures 1, 2). Characteristics of patients are summarised in the appendix. Qualitative interviews, lasting a mean of 135 min (SD 39), were completed with 101 of 103 health-care professionals, resulting in 101 transcriptions (roughly 40000 words each). 23 of 34 hospitals in the study regions agreed to participate (8964 of 11033 [81·2%] beds).

2016 of the 5147 (39·2%) patients surveyed who died of cancer in the study regions in the preintervention period died at participating institutions, and 2212 of 5546 (39·9%) patients surveyed during the post-intervention period died at participating institutions.

Table 1 summarises the coverage of interventions during the study. 355 of 706 (50·3%) physicians and 994 of 2236 (44·5%) nurses participated at least once in an interactive workshop or a whole-region interdisciplinary conference, or both, and 517 of 706 (73·2%) physicians and 1512 of 2236 (67·6%) nurses used or acknowledged the manual or assessment instruments, or both.

In 2007, four palliative care units, ten hospital or community palliative care teams, five outpatient palliative care services, and no home palliative care teams were available. In 2010, after the interventions, five palliative care units, 11 hospital or community palliative care teams, 11 outpatient palliative care services, and two home palliative care teams were available. All services were maintained after the study.

The proportion of patients that died at home was significantly higher after than before the interventions (p<0·0001; table 2), and this increase was significantly greater than that noted in the national reference data (p<0·0001; figure 3). The ratio of patients who received palliative care services to patients who died of cancer (p<0·0001), and patient-reported (adjusted p=0·0027) and family-reported (p<0·0001) qualities of palliative care increased significantly from before the interventions to after the interventions.

In the postintervention surveys, of 581 patients who died at home, 311 family members were identified and sent questionnaires, and 221 returned completed questionnaires. 194 (87·78%) of the responding family members agreed or strongly agreed that the patient had died in his or her preferred place, and an additional nine (4·07%) slightly agreed. Furthermore, the care burden did not change significantly during the study period (for either all families or families of patients who died at home; table 2). Significantly fewer patients spent more than 2 weeks of the last month of their lives in hospital after the interventions than before the interventions (p<0·0001; table 2).

| | Before interventions | After interventions | Effect size | p | Adjusted p |
|---|---|---|---|---|---|
| **Primary endpoints** | | | | | |
| Home deaths | 348/5147 (6·76%) | 581/5546 (10·48%) | .. | <0·0001 | .. |
| Ratios of patients who received specialised palliative care services to patients who died from cancer* | 0·31 | 0·50 | .. | <0·0001 | .. |
| Quality of palliative care† | | | | | |
| Patient-reported | 4·43 (1·08) | 4·57 (0·97) | 0·14 | 0·0055 | 0·0027 |
| Family-reported | 4·31 (1·12) | 4·56 (1·08) | 0·23 | <0·0001 | <0·0001 |
| **Secondary endpoints** | | | | | |
| Care burden‡ | | | | | |
| Total | 3·97 (1·50) | 4·03 (1·50) | 0·04 | 0·3546 | .. |
| Families of patients who died at home | 3·76 (1·57) | 3·87 (1·54) | 0·07 | 0·5874 | .. |
| 2 weeks or more in hospital in the last month of life | 744/1039 (71·61%) | 677/1061 (63·81%) | .. | <0·0001 | .. |
| Quality of life§ | | | | | |
| Patient-reported | 5·45 (0·98) | 5·52 (0·92) | 0·08 | 0·1024 | 0·1680 |
| Family-reported | 4·41 (0·97) | 4·63 (0·96) | 0·22 | <0·0001 | <0·0001 |
| Physician-reported difficulty¶ | | | | | |
| Total | 2·69 (0·80) | 2·28 (0·75) | 0·52 | <0·0001 | <0·0001 |
| Communication in multidisciplinary teams | 2·47 (1·05) | 2·10 (0·97) | 0·37 | <0·0001 | <0·0001 |
| Community coordination | 2·96 (1·15) | 2·25 (1·08) | 0·63 | <0·0001 | <0·0001 |
| Expert support | 2·40 (1·25) | 1·83 (1·06) | 0·49 | <0·0001 | <0·0001 |
| Alleviation of symptoms | 2·94 (0·98) | 2·76 (0·98) | 0·18 | <0·0001 | <0·0001 |
| Communication with patients | 2·66 (0·94) | 2·45 (0·92) | 0·22 | <0·0001 | <0·0001 |
| Physician-reported knowledge‖ | 72·00 (22·86) | 78·46 (20·35) | 0·30 | <0·0001 | <0·0001 |
| Nurse-reported difficulty¶ | | | | | |
| Total | 3·15 (0·75) | 2·72 (0·73) | 0·59 | <0·0001 | <0·0001 |
| Communication in multidisciplinary teams | 3·09 (1·03) | 2·65 (1·05) | 0·42 | <0·0001 | <0·0001 |
| Community coordination | 3·03 (1·16) | 2·37 (1·05) | 0·60 | <0·0001 | <0·0001 |
| Expert support | 2·90 (1·30) | 2·19 (1·14) | 0·58 | <0·0001 | <0·0001 |
| Alleviation of symptoms | 3·49 (0·84) | 3·28 (0·88) | 0·24 | <0·0001 | <0·0001 |
| Communication with patients | 3·25 (0·91) | 3·07 (0·97) | 0·19 | <0·0001 | <0·0001 |
| Nurse-reported knowledge‖ | 50·72 (20·16) | 60·43 (21·89) | 0·46 | <0·0001 | <0·0001 |

Data are n/N (%) or mean score (SD) unless otherwise specified. *N=1606 before the intervention and 2783 after the intervention. †Measured with the care evaluation scale, which ranges from 1 to 6 (high score suggests low perception of necessity for improvement). ‡Measured with the caregiving consequences inventory, which ranges from 1 to 7 (high score suggests low perceived care burden). §Measured with the good death inventory, which ranges from 1 to 7 (high score suggests a high perceived quality of life). ¶Measured with the palliative care difficulty scale, which ranges from 1 to 5 (high score suggests a high level of perceived difficulties). ‖Measured with the palliative care knowledge test, which ranges from 0 to 100 (high score suggests high level of accurate knowledge).

*Table 2:* **Summary of endpoints before and after programme of interventions**

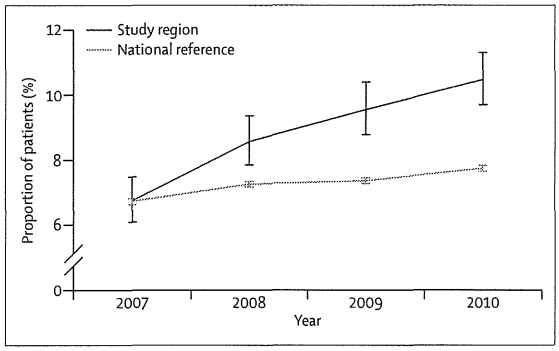


*Figure 3:* **Proportion of patients with cancer who died at home after the programme of interventions compared with national standards**
Bars are 95% CIs. In study regions, 348 of the 5147 (6·8%) total cancer deaths in 2007, 463 of the 5394 (8·6%) total cancer deaths in 2008, 507 of the 5302 (9·6%) total cancer deaths in 2009, and 581 of the 5546 (10·5%) total cancer deaths in 2010 were home deaths. In national reference data, 22 623 of the 336 468 (6·7%) total cancer deaths in 2007, 24 941 of the 342 963 (7·3%) total cancer deaths in 2008, 25 433 of the 344 105 (7·4%) total cancer deaths in 2009, and 27 508 of the 353 499 (7·8%) total cancer deaths in 2010 were home deaths.

Family-reported quality of life of terminally ill patients was significantly higher after than before the interventions (adjusted p<0·0001), whereas patient-reported quality of life did not significantly change (p=0·1680; table 2). Physician-reported and nurse-reported difficulties in delivering palliative care decreased significantly after the interventions (p<0·0001), with overall effect sizes of more than 0·5 (table 2). Physician-reported and nurse-reported knowledge increased significantly after the interventions (table 2). Greater improvements were noted in the subscales of community coordination, expert support, and communication in multidisciplinary teams (table 2).

Through analysis of the qualitative data, we identified seven themes, typical data for three of which are included in the appendix. The health-care professionals who had roles in the implementation of the interventions greatly emphasised improved communication and cooperation between regional health-care professionals (data not shown) and described various ways in which communication and cooperation improved daily palliative care practices—eg, many meetings were held at which specialists and responsible persons were more easily contactable than they had been previously. The main perceived reasons for changes were whole-region interdisciplinary conferences and informal interactions at various meetings (data not shown).

Implementing health-care professionals also perceived increased confidence in the system to care for patients with cancer at home (data not shown). Changes were identified both in hospitals and the community, and the implementing health-care professionals stated that these changes resulted in timely discharge to home or a longer stay at home, or both (data not shown). Perceived reasons for these changes included collaboration with various specialties, easier exchange of information, increased availability of specialists and inpatient resources, development of discharge-planning divisions, and improved hospital clinicians' knowledge about what care was provided at home and community clinicians' general improved knowledge (data not shown).

## Discussion

Our study was one of the largest and most comprehensive mixed-methods studies to explore the effects of a region-wide programme of interventions to improve palliative care for patients with cancer (panel 2). We measured interpretable multidimensional outcomes from a large population (that was nearly representative of the regions involved), and introduced interventions that could be adopted in other regions. The qualitative study, furthermore, suggests a framework for how this change occurred, and this framework can guide researchers and policy makers designing interventions to improve region-based palliative care.

Introduction of the interventions increased the proportion of deaths occurring at home—a result consistent with the findings of a previous randomised study,[4] which did not, however, assess whether the increase in the rate of home deaths was associated with the patients' preferences or those of their families. A strength of our study was that most family members of patients who died at home confirmed that the patient wanted to die at home. Furthermore, we noted no evidence of increases in the care burden of families of patients who died at home. The absolute number of home deaths was, nonetheless, still low after the interventions, suggesting that some structural or financial changes are needed in the health-care system before a further increase in the proportion of home deaths will occur.

Significant improvements in patient-reported and family-reported qualities of care and family-reported quality of life were noted, but changes in patients' outcomes were generally small, probably because the high scores of outpatients in the preintervention survey caused ceiling effects and interventions were mainly targeted to patients with more advanced cancer.

Importantly, the intervention programme significantly decreased difficulties associated with delivering palliative care reported by physicians and nurses at a regional level, especially those related to communication, coordination, and expert support. This finding was strongly supported by the qualitative findings, which showed that communication and cooperation were particularly improved, suggesting that one of the most powerful perceived effects is improved communication between health-care professionals.[10–13]

An additional strength of the qualitative study was that many ways in which good communication and cooperation can positively affect daily practice and patients' outcomes were clearly described. The key interventions cited were whole-region interdisciplinary conferences and informal interactions at various types of

*Panel 2:* **Research in context**

**Systematic review**

We searched PubMed and palliative care journals (*Journal of Pain and Symptom Management*, *Palliative Medicine*, *Journal of Palliative Medicine*, and *Supportive Care in Cancer*) with the terms ((“palliative care” [MeSH Terms] OR “palliative care”[All Fields]) OR “end-of-life” [All Fields]) AND (“region” [All Fields] OR “population-based” [All Fields] OR “community” [All Fields]) for articles published between Jan 1, 1990, and Jan 31, 2013. We identified four series of studies assessing regional palliative care programmes. The earliest work was about the development of a regional palliative care programme in Edmonton (AB, Canada).[7] Later, a cluster-randomised controlled trial[4,5] was done in Norway. We also identified quality-improvement projects with no control groups in Spain[6,9] and Ontario, Canada.[8] The results of these studies suggested that a programme of interventions has positive effects on some outcomes for regional palliative care delivery, including place of death. However, the comprehensive effects of such a programme on an entire region are poorly understood, because no studies have comprehensively assessed a representative sample of patients, bereaved family members, and health-care professionals throughout a region. Furthermore, no studies were based on a mixed-methods design to explore how these changes occurred.

**Interpretation**

Our study clarified the effects of a programme of regional palliative care interventions on a range of outcomes, including place of death, use of specialised palliative care services, patient-perceived and family-perceived quality of care, patients’ quality of life, family care burden, and physician-perceived and nurse-perceived difficulties and knowledge. Although the programme of interventions had an overall benefit, the largest effect in both quantitative and qualitative studies was improved communication between health-care professionals. Our study adds important insights about the comprehensive effect of regional palliative care programmes and the crucial value of communication between health-care professionals to improve palliative care at a regional level.

meeting. These findings provide insight into why improved communication is important for high-quality palliative care at a regional level and strongly imply that easing communication between health-care professionals is essential for improvement of regional palliative care.

Our study had some substantial limitations, the most important of which was the absence of a control group (excepting people who died at home and were included in national data). Second, the outcomes measured with questionnaire surveys might have been affected by selection, response, and recall biases. Although we statistically adjusted for all noted differences in participants’ backgrounds, the intervention effects might have been overestimated, especially in the samples of patients and bereaved families, because of an unexplained increase in excluded participants as a result of severe emotional distress and an increase in sampling from home settings. These methodological limitations can be overcome in future studies through use of, when feasible, data from complete patients’ registries or a mortality follow-back survey, or both. Third, our data might not be a fully representative regional sample, although most hospital beds and roughly 40% of deceased patients were included. Fourth, we did not measure objective metrics of health-service use (eg, number of admissions). Fifth, patients who received medical care from an institution within 2 days or who were not informed of malignancy (and their families) did not have input. Finally, we excluded patients who did not have cancer.

As a policy implication, establishment of a structure to improve communication between health-care professionals is an extremely important element of regional palliative care programmes. We recommend the use of combined methods to understand the overall effects of region-wide multicomponent interventions.

**Contributors**

TM drafted the paper and had roles in data collection and study conception and design. MM and TY contributed to data analysis and interpretation and study conception and design. AY, NA, YS, and MA contributed to study conception and design, data collection, and critical revision of the article for important intellectual content. YK and KH contributed to study conception and design and critical revision of the article for important intellectual content. CI contributed to study conception and design and data analyses of the qualitative study. MK and KE contributed to study conception and design, critical revision of the article for important intellectual content, and organisation of the research team.

**Conflicts of interest**

We declare that we have no conflicts of interest.

**Acknowledgments**

This study was funded by the Third Term Comprehensive Control Research for Cancer Health and Labor Sciences Research Grants in Japan. We thank Shohei Kawagoe, Hiroya Kinoshita, Kazuki Sato, Satoshi Suzuki, Toru Takebayashi, Motohiro Matoba, Megumi Umeda, Masako Yamada, and Sen Yamakawa for their contributions as essential members of the research team; Yoichi Matsubara, Takeshi Mishina, Hiroyasu Esumi, Kazunori Ogino, Hisao Morooka, and Takatoshi Noda for managing research regions; Tomoko Matsumura for broad assistance in the organisation of the research team; and Masao Okazaki for help with medical writing.

**References**

1 WHO. National cancer control programs: policies and managerial guidelines, 2nd edn. Geneva: World Health Organization, 2002.
2 Higginson IJ, Finlay I, Goodwin DM, et al. Do hospital-based palliative teams improve care for patients or families at the end of life? *J Pain Symptom Manage* 2002; **23**: 96–106.
3 Higginson IJ, Finlay IG, Goodwin DM, et al. Is there evidence that palliative care teams alter end-of-life experiences of patients and their caregivers? *J Pain Symptom Manage* 2003; **25**: 150–168.
4 Jordhøy MS, Fayers P, Saltnes T, Ahlner-Elmqvist M, Jannert M, Kaasa S. A palliative-care intervention and death at home: a cluster randomised trial. *Lancet* 2000; **356**: 888–93.
5 Jordhøy MS, Fayers P, Loge JH, Ahlner-Elmqvist M, Kaasa S. Quality of life in palliative cancer care: results from a cluster randomized trial. *J Clin Oncol* 2001; **19**: 3884–94.

6 Herrera E, Rocafort J, De Lima L, Bruera E, García-Peña F, Fernández-Vara G. Regional palliative care programme in Extremadura: an effective public health care model in a sparsely populated region. *J Pain Symptom Manage* 2007; **33:** 591–98.

7 Fassbender K, Fainsinger R, Brenneis C, Brown P, Braun T, Jacobs P. Utilization and costs of the introduction of system-wide palliative care in Alberta, 1993–2000. *Palliat Med* 2005; **19:** 513–20.

8 Gilbert JE, Howell D, King S, et al. Quality improvement in cancer symptom assessment and control: the Provincial Palliative Care Integration Project (PPCIP). *J Pain Symptom Manage* 2012; **43:** 663–78.

9 Gómez-Batiste X, Caja C, Espinosa J, et al. The Catalonia World Health Organization demonstration project for palliative care implementation: quantitative and qualitative results at 20 years. *J Pain Symptom Manage* 2012; **43:** 783–94.

10 Shaw KL, Clifford C, Thomas K, Meehan H. Improving end-of-life care: a critical review of the Gold Standards Framework in primary care. *Palliat Med* 2010; **24:** 317–29.

11 Masso M, Owen A. Linkage, coordination and integration. Evidence from rural palliative care. *Aust J Rural Health* 2009; **17:** 263–67.

12 Kelley ML. Developing rural communities' capacity for palliative care: a conceptual model. *J Palliat Care* 2007; **23:** 143–53.

13 Nikbakht-Van de Sande CV, van der Rijt CC, Visser AP, ten Voorde MA, Pruyn JF. Function of local networks in palliative care: a Dutch view. *J Palliat Med* 2005; **8:** 808–16.

14 Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M; Medical Research Council Guidance. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008; **337:** a1655.

15 Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M; Medical Research Council Guidance. Developing and evaluating complex interventions: new guidance. http://www.mrc.ac.uk/complexinterventionsguidance (accessed March 10, 2013).

16 Ikegami N, Yoo B-K, Hashimoto H, et al. Japanese universal health coverage: evolution, achievements, and challenges. *Lancet* 2011; **378:** 1106–15.

17 Tsuneto S. Past, present, and future of palliative care in Japan. *Jpn J Clin Oncol* 2013; **43:** 17–21.

18 Yamagishi A, Morita T, Miyashita M, et al. Palliative care in Japan: current status and a nationwide challenge to improve palliative care by the Cancer Control Act and the Outreach Palliative Care Trial of Integrated Regional Model (OPTIM) study. *Am J Hosp Palliat Med* 2008; **25:** 412–18.

19 Morita T, Miyashita M, Yamagishi A, et al. A region-based palliative care intervention trial using the mixed-method approach: Japan OPTIM study. *BMC Palliat Care* 2012; **11:** 2.

20 Morita T, Hirai K, Sakaguchi Y, Maeyama E, Tsuneto S, Shima Y. Measuring the quality of structure and process in end-of-life care from the bereaved family perspective. *J Pain Symptom Manage* 2004; **27:** 492–501.

21 Miyashita M, Wada M, Morita T, Matoba M, Tsuneto S, Shima Y. Reliability and validity of the care evaluation scale patient version. 15th Congress of Japanese Society of Palliative Medicine; Tokyo, Japan; June 18–19, 2010. 09-4.

22 Sanjo M, Morita T, Miyashita M, et al. Caregiving consequences inventory: a measure for evaluating caregiving consequences from the bereaved family member's perspective. *Psychooncology* 2009; **18:** 657–66.

23 Miyashita M, Morita T, Sato K, et al. Good death inventory: a measure for evaluating good death from the bereaved family member's perspective. *J Pain Symptom Manage* 2008; **35:** 486–98.

24 Miyashita M, Wada M, Morita T, Matoba M, Tsuneto S, Shima Y. Reliability and validity of the good death inventory patient version. 15th Congress of Japanese Society of Palliative Medicine; Tokyo, Japan; June 18–19, 2010. 09-5.

25 Nakazawa Y, Miyashita M, Morita T, Umeda M, Oyagi Y, Ogasawara T. The palliative care self-reported practices scale and the palliative care difficulties scale: reliability and validity of two scales evaluating self-reported practices and difficulties experienced in palliative care by health professionals. *J Palliat Med* 2010; **13:** 427–37.

26 Nakazawa Y, Miyashita M, Morita T, Umeda M, Oyagi Y, Ogasawara T. The palliative care knowledge test: reliability and validity of an instrument to measure palliative care knowledge among health professionals. *Palliat Med* 2009; **23:** 754–66.

27 Pope C, Ziebland S, Mays N. Qualitative research in health care. Analysing qualitative data. *BMJ* 2000; **320:** 114–16.

28 Creswell JW. Research design: qualitative, quantitative, and mixed methods approaches, 3rd edn. Thousand Oaks, CA: Sage, 2009.

29 Hedges LV, Olkin I. Statistical methods for meta-analysis. Orlando, FL: Academic Press, 1985.

30 Cohen J. A power primer. *Psychol Bull* 1992; **112:** 155–59.