Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Morita T, Sato K, Miyashita M, Yamagishi A, Kizawa Y, Shima Y, Kinoshita H, Suzuki S, Shirahige Y, Yamaguchi T, Eguchi K.	Does a regional comprehensive palliative care program improve pain in outpatient cancer patients?	Support Care Cancer.	22(9)	2444-2455	2014,
Kanbayashi Y, Hosokawa T.	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?	J Palliat Med.	17(6)	683-687	2014

（註）研究責任者、研究責任者の平成２６年度の研究発表については、総括研究報告書の研究発表欄に代表的な業績目録を掲載したので参照されたい。研究成果の刊行に関する一覧表およびその別刷については、誌面の都合上、本研究と深く関わりのある代表的な文献の掲載にとどめ、その他の文献については割愛させていただいた。なお、本研究は本報告書作成時点で追加調査が進行中であり、その調査が終わり次第、国内外の学会での学会発表、論文発表を行い、さらに成果を発信する予定である。

Ⅳ. 研究成果の刊行物・別刷

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Prospective Clarification of the Utility of the Palliative Prognostic Index for Patients With Advanced Cancer in the Home Care Setting

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Abstract

Aims: This study aimed to prospectively clarify the accuracy of the Palliative Prognostic Index (PPI) for advanced cancer patients in home care settings. **Method:** The study included 66 advanced cancer patients who received home visiting services between April 2010 and June 2012, and who died at home or in the hospital. Using medical records from initial home visits, we prospectively calculated PPI scores along with sensitivity and specificity. **Results:** For 3- and 6-week survival, prognostic prediction showed respective sensitivities of 60% and 70.6%, and specificities of 87.0% and 71.9%. **Conclusion:** The sensitivity of the PPI for advanced cancer patients in home care settings was lower than that reported for patients in palliative care units. Development of prognostic tools suitable for home care settings is needed.

Keywords

palliative prognostic index, patients with advanced cancer, home care setting, prospective study, prognostic prediction, palliative care

Introduction

Making prognostic predictions is one of the core skills of physicians engaged in end-of-life care[1] and is a component of approaches to multidisciplinary palliative care.[2] In addition, patients with advanced cancer face difficult decisions regarding their treatment and choices related to end-of-life care.[3,4] Accurately predicting prognosis is therefore helpful not only for patients and their families but also for health care professionals who support their decision making,[5] especially those in the home care setting.

In general, it is difficult to predict the prognosis of patients with advanced cancer, especially those in the home care setting, because of limitations in the number of blood tests and radiological evaluations performed. Clinicians usually predict prognoses based on their own experience. A previous study revealed that prognostic prediction tools improved the accuracy of physicians' predictions.[6] Several prognostic prediction tools have been examined for patients with cancer, for example the Palliative Prognostic Index (PPI),[7] Cancer Prognostic Scale,[7] Palliative Performance Scale (PPS),[8] Palliative Prognostic Score (PaP score),[9] PaP Score with Delirium,[10] Japan Palliative Oncology Study-Prognostic Index,[11] and Prognosis in Palliative Care Study model,[12] and each was properly validated. These tools are intended for use in assessing inpatient and ambulatory patients, and the appropriateness of their application to patients with advanced cancer in the home care setting is uncertain.

The PPI, which resulted in significant improvement in prognostication,[6] was defined based on the performance status assessment using the PPS version 2 (PPSv2),[8] oral intake, and the presence or absence of dyspnea at rest, edema, and delirium. The PPI was developed and successfully validated for patients with cancer in palliative care units by Morita et al in Japan.[13]

The PPI does not require blood tests or radiological evaluation and would therefore be very useful for patients with cancer in the home care setting when compared to other validated

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prognostic prediction tools. Each PPI component is assigned an individual score, and these are added to derive the overall score. The final PPI score classifies patients into 1 of the 3 groups, those with survival predicted to be shorter than 3 weeks (PPI $\geq$ 6), shorter than 6 weeks (PPI $\geq$ 4), or longer than 6 weeks (PPI < 4).

Previous studies[14] were performed prospectively and did not clarify the usefulness of the PPI in the home care setting. The aims of this study were thus to prospectively determine the sensitivity and specificity of the PPI in the home care setting and to evaluate the association of each PPI component with 3 and 6 weeks' prognostic prediction.

Methods

Our study population included all patients with advanced cancer who received home visiting services regularly from Yamato Clinic between April 2010 and June 2012 and who died at home or in the hospital. Yamato Clinic provides ambulatory care and home visiting services for community residents, with 3 doctors (including 1 researcher: JH) specialized in family medicine and palliative care. The 3 doctors (including 1 researcher: JH) had trained to assess the PPI components and used the PPI in their usual practice. We recorded patients' background information and prospectively assessed the components of the PPI at the first home visit, PPS score, oral intake, and the presence or absence of dyspnea at rest, edema, and delirium. One researcher (JH) calculated the PPI score and actual survival time when each patient died. Subsequently, we calculated overall sensitivity, specificity, and area under the curve (AUC) of the PPI. Survival predictions were defined as mentioned earlier, less than 3 weeks for PPI $\geq$ 6 and less than 6 weeks for PPI $\geq$ 4. In addition, we conducted univariable analyses to assess significant differences between 3- and 6-week survival and each PPI component.

To determine the association of each PPI component with 3 and 6 weeks' prognostic prediction, we used Student *t* test for continuous variables and Pearson chi-square test or Fisher exact test for categorical variables. All analyses were conducted using SPSS-J, ver.21.0, IBM (Tokyo, Japan).

This study was not confirmed by the institutional review board, but our study was performed according to the ethical guidelines for Epidemiological Research by the Ministry of Health, Labour and Welfare of Japan, and written informed consent was not necessary.

This study was conducted in conformity with the Declaration of Helsinki and was carried out with special regard for the protection of individual data.

Results

A total of 66 (48 males) patients were included in this study. Table 1 shows the patient background information in detail. The mean patient age was 75.6 years, with 28 (42.4%) patients in their 70s and 15 (22.7%) patients in their 80s. The primary cancer site was lung in 17 (15.8%) patients, stomach/esophagus

Table 1. Patient Background (n = 66).

	All patients (n = 66), n (%)
Gender	
Male	48 (72.7)
Female	18 (27.3)
Mean age (year ± SD)	75.6 ± 11.3
Range, years	41–94
Age distribution	
35-49	3 (4.5)
50-59	1 (1.5)
60-69	12 (18.2)
70-79	28 (42.4)
80-89	15 (22.7)
90+	7 (10.6)
Primary cancer site	
Lung	17 (25.8)
Stomach/esophagus	12 (18.2)
Colon/rectum/anus	10 (15.2)
Kidney/bladder	6 (9.1)
Liver/biliary system	6 (9.1)
Pancreas	4 (6.1)
Prostate	3 (4.5)
Brain	3 (4.5)
Breast	1 (1.5)
Blood	1 (1.5)
Others	3 (4.5)

Abbreviation: SD, standard deviation.

Table 2. The PPI Scores and 3-Week Survival.

	<3 weeks' survival	≥3 weeks' survival	Total
PPI ≥ 6	12[a]	6	18
PPI < 6	8	40	48
Total	20	46	66

Abbreviation: PPI, Palliative Prognostic Index.
[a] Number of patients surviving <3 weeks with PPI scores >6.

Table 3. The PPI Scores and 6-Week Survival.

	<6 weeks' survival	≥6 weeks' survival	Total
PPI ≥ 4	24[a]	9	33
PPI < 4	10	23	33
Total	34	32	66

Abbreviation: PPI, Palliative Prognostic Index.
[a] Number of patients surviving <6 weeks with PPI scores >4.

Table 4. Accuracy of PPI for Patients With Advanced Cancer in Home Care Settings.

	<3 weeks, %	<6 weeks, %
Sensitivity	60.0	70.6
Specificity	87.0	71.9
Positive predictive value	66.7	72.7
Negative predictive value	83.3	69.7
Area under the curve	74	67

Abbreviation: PPI, Palliative Prognostic Index.

Table 5. Univariable Analyses for Patients Surviving <3 Weeks and 6 Weeks (n = 66).

Variable	<3 weeks' survival (n = 20), n (%)	≥3 weeks' survival (n = 46), n (%)	*P* value	<6 weeks' survival (n = 34), n (%)	≥6 weeks' survival (n = 32), n (%)	*P* value
Mean age (year ± SD)	73.1 ± 10.7	76.6 ± 11.5	.25[a]	72.4 ± 10.4	78.9 ± 11.4	.019[a]
Sex						
Male	15 (75.0)	33 (71.7)	.785[b]	26 (76.5)	22 (68.8)	.482[b]
Female	5 (25.0)	13 (28.3)		8 (23.5)	10 (31.3)	
Palliative Performance Scale version 2 (PPSv2)[8]						
10-20	3 (15.0)	0	.01[c]	3 (8.8)	0	.001[c]
30-50	16 (80.0)	36 (78.3)		30 (88.2)	22 (68.8)	
60+	1 (5.0)	10 (21.7)		1 (2.9)	10 (31.3)	
Oral intake						
Severely reduced	8 (40.0)	1 (2.2)	<.01[c]	8 (23.5)	1 (3.1)	.006[c]
Moderately reduced	12 (60.0)	31 (67.4)		23 (67.6)	20 (62.5)	
Normal	0	14 (30.4)		3 (8.8)	11 (34.4)	
Edema						
Present	11 (55.0)	16 (34.8)	.125[b]	17 (50.0)	10 (31.3)	.122[b]
Absent	9 (45.0)	30 (65.2)		17 (50.0)	22 (68.8)	
Dyspnea at rest						
Present	8 (40.0)	3 (6.5)	.002[b]	9 (26.5)	2 (6.3)	.028[b]
Absent	12 (60.0)	43 (93.5)		25 (73.5)	30 (93.8)	
Delirium						
Present	8 (40.0)	4 (8.7)	.005[c]	11 (32.4)	1 (3.1)	.002[b]
Absent	12 (60.0)	42 (91.3)		23 (67.6)	31 (96.9)	

Abbreviation: SD, standard deviation.
[a] Student *t* test.
[b] Pearson chi-square test.
[c] Fisher exact test.

in 12 (18.2%) patients, and colon/rectum/anus in 10 (15.2%) patients.

The mean survival time after the first home visit was 72.9 days. Survival time was shorter than 3 weeks in 20 (30.3%) patients and shorter than 6 weeks in 34 (51.5%) patients. Table 2 shows PPI scores and 3-week survival, and Table 3 shows PPI scores and 6-week survival. In all, 18 (27.3%) patients had PPI scores ≥6, while 33 (50%) had PPI scores ≥4. In all, 12 patients with PPI scores ≥6 survived for less than 3 weeks, while 24 patients with PPI scores ≥4 survived for less than 6 weeks.

Table 4 shows the accuracy of the PPI for patients with advanced cancer in the home care setting. Three-week survival was predicted with a sensitivity of 60% (95% confidence interval [CI], 39%-78%), a specificity of 86.9% (95% CI, 74%-94%), a positive predictive value of 66.7%, and a negative predictive value of 83.3%; the AUC was 74% (95% CI, 59%-88%). Six-week survival was predicted with a sensitivity of 70.6% (95% CI, 54%-83%), a specificity of 71.9% (95% CI, 55%-84%), a positive predictive value of 72.7%, and a negative predictive value of 69.7%; the AUC was 67% (95% CI, 54%-81%).

Table 5 shows the association of each PPI component with 3 and 6 weeks' prognostic prediction. We conducted univariable analyses concerning PPI components for patients who survived less than 3 weeks and less than 6 weeks. These analyses found that PPS, oral intake, dyspnea at rest, and delirium were statistically significant for patients who survived less than 3 weeks and less than 6 weeks.

Discussion

This study demonstrated 3 important findings. First, the sensitivity of the PPI for patients with advanced cancer in the home care setting was lower than for patients with advanced cancer in palliative care units. Morita et al[13] reported that the sensitivity of the PPI for patients with advanced cancer in the hospice setting who survived less than 3 weeks and less than 6 weeks was 83% and 79%, respectively. This finding is same as that of our previous retrospective study.[15] Maltoni et al[16] also reported a prospective comparison between several prognostic scores, including the PPI, in the hospice setting. They found that the sensitivity and specificity of PPI scores ≥5 in patients who survived for less than 3 weeks in the hospice setting were 73.7% and 67.1%, respectively. To the best of our knowledge, however, our study is the first to prospectively reveal the usefulness of the PPI for patients with advanced cancer in the home care setting while also pointing out the limitations of the utility of the PPI in this population and setting.

One possible reason for the discrepancy in PPI sensitivity between patients with advanced cancer in the hospice setting and those in the home care setting is the differential prevalence of PPS ≤20 and delirium, which are the most heavily weighted scores in the PPI scoring system. In our study, the prevalence of

PPS ≤20 in the home care setting was 4.5%, whereas Morita et al[13] and Maltoni et al[16] reported prevalence of 23% and 41.3%, respectively, in the hospice setting. This discrepancy suggests the possibility that home visiting services tend to be started at early stages for patients with advanced cancer, because whilethe median duration of survival was 40 days in our study, Morita et al[13] reported 27 days and Maltoni et al[16] reported 22 days in the hospice setting. Regarding the prevalence of delirium, our study revealed a prevalence of 18.2% in the home care setting, whereas Morita et al[13] and Maltoni et al[16] reported prevalence of 38% and 28.2%, respectively, in the hospice setting. This discrepancy may have 2 causes. First, we may have underdiagnosed delirium because we did not use routinely a specific assessment tool for its screening. Second, patients who have delirium may tend not to transfer from hospital to home care, because management of delirium is commonly difficult in the home care setting. The prevalence of other symptoms in our study, namely, oral intake, edema, and dyspnea at rest, also differed compared to the hospice setting. In our study, the prevalence of severely reduced oral intake, edema, and dyspnea at rest were 13.6%, 40.9%, and 16.7%, respectively, although Morita et al[13] reported prevalence of 38%, 35.4%, and 18% and Maltoni et al[16] reported prevalence of 27.7%, 33%, and 24.4%, respectively. These discrepancies may suggest that patient background differs intrinsically between the home care setting and the hospice setting. Therefore, the low sensitivity of the PPI means that this instrument may not be suitable for detecting poor prognosis in patients with relatively good performance status, especially in the home care setting. In addition to the results mentioned earlier, we found that the specificity of PPI for patients with advanced cancer in the home care setting was nearly 90% in our study for 3-week survival, the same as in our previous study.[15] These results support our previous suggestion that the PPI might not be useful as a screening tool for poor prognosis in the home care setting because of its low sensitivity but might be useful with PPI scores <6, predicting survival longer than 3 weeks.

The second important finding of this study was that PPS, oral intake, dyspnea at rest, and delirium had statistically significant associations with survival durations of less than 3 weeks and less than 6 weeks for patients with advanced cancer in the home care setting, while edema showed no significant correlation. This finding is in accordance with the European Association for Palliative Care recommendations regarding prognostic factors.[2] It is possible that no association was detected between edema and survival due to insufficient power resulting from the small sample size of this study. We must reevaluate this question using a larger sample size from this patient population before forming a definitive conclusion, because a previous study[11] showed that edema was significantly related to patient survival in the hospital setting.

The last important finding of this study was that all 14 patients with normal oral intake survived longer than 3 weeks. One possible reason may be that the nutritional status of the current study, patients with normal intake, was maintained better than that of patients in previous studies using inpatient settings. In the home care setting, patients can eat their favorite foods whenever they want, making it more likely that they can maintain a normal oral intake which may lead to prolonged survival. A corollary to this is that there may be several disadvantages to using oral intake as a factor in predicting prognosis in the inpatient setting; for example, patients may not be served meals they like, and they may not express their meal preferences as easily as in the home care setting. Therefore, we may mistakenly judge that patients in the inpatient setting may have decreased oral intake when in another setting they would in fact have normal oral intake.

This study has 3 limitations. First, our report may not be representative of patients with advanced cancer in the home care setting, because it was carried out only in 1 institution. Second, the population of this study was relatively small. These limitations restrict the generalizability of our results. Third, as we have already described, we may have underdiagnosed delirium because we did not screen using a standardized specific assessment tool such as Confusion Assessment Method.[17] This may affect the accuracy of the PPI in the current study. To overcome these limitations, we should carry out a large multicenter study for patients with advanced cancer using standard symptom assessment tools in the home care setting.

In conclusion, this study showed that the PPI had a lower sensitivity for patients with advanced cancer in the home care setting than for those in palliative care units, although the specificity of the PPI for patients with advanced cancer in the home care setting was nearly 90% for 3-week survival. Further research is needed to develop more accurate prognostic prediction tools for use in the home care setting.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Glare PA, Sinclair CT. Palliative medicine review: prognostication. *J Palliat Med.* 2008;11(1):84-103.
2. Maltoni M, Caraceni A, Brunelli C, et al. Prognostic factors in advanced cancer patients: evidence-based clinical recommendations—a study by the steering committee of the European Association for Palliative Care. *J Clin Oncol.* 2005;23(25):6240-6248.
3. Finlay E, David C. Making difficult discussions easier: using prognosis to facilitate transitions to hospice. *CA Cancer J Clin.* 2009;59(4):250-263.
4. Yoong J, Atkin N, Le B. Use of the palliative prognostic index in a palliative care consultation service in Melbourne, Australia. *J Pain Symptom Manage.* 2010;39(1):e2-e4.

5. Stone PC, Lund S. Predicting prognosis in patients with advanced cancer. *Ann Oncol.* 2007;18(6):971-976.
6. Morita T, Tsunoda J, Inoue S, Chihara S. Improved accuracy of physicians' survival prediction for terminally ill cancer patients using the palliative prognostic index. *Palliat Med.* 2001;15(5): 419-424.
7. Lau F, Cloutier-Fisher D, Kuziemsky C, et al. A systematic review of prognostic tools for estimating survival time in palliative care. *J Palliat Care.* 2007;23(2):93-112.
8. Palliative Performance Scale (PPSv2) version 2. http://www.victoriahospice.org/sites/default/files/pps_japanese.pdf. Accessed May 5, 2013.
9. Glare PA, Eychmueller S, McMahon P. Diagnostic accuracy of the palliative prognostic score in hospitalized patients with advanced cancer. *J Clin Oncol.* 2004;22(23);4823-4828.
10. Scarpi E, Marco M, Rosalba M, et al. Survival prediction for terminally Ill cancer patients: revision of the palliative prognostic score with incorporation of delirium. *Oncologist.* 2011;16(12): 1793-1799.
11. Hyodo I, Morita T, Adachi I, Shima Y, Yoshizawa A, Hiraga K. Development of a predicting tool for survival of terminally ill cancer patients. *Jpn J Clin Oncol.* 2010;40(5):442-448.
12. Gwilliam B, Keeley V, Todd C, et al. Development of prognosis in palliative care study (PiPS) predictor models to improve prognostication in advanced cancer: prospective cohort study. *BMJ.* 2011;343:d4920.
13. Morita T, Tsunoda J, Inoue S, Chihara S. The palliative prognostic index: a scoring system for survival prediction of terminally ill cancer patients. *Support Care Cancer.* 1999; 7(3):128-133.
14. Stone CA, Tiernan E, Dooley BA. Prospective validation of the palliative prognostic index in patients with cancer. *J Pain Symptom Manage.* 2008:35(6):617-622.
15. Hamano J, Maeno T, Kizawa Y, Shima Y, Maeno T. Usefulness of palliative prognostic index for patient with advanced cancer in home care setting. *Am J Hosp Palliat Care.* 2013:30(3): 260-263.
16. Maltoni M, Scarpi E, Pittureri C, et al. Prospective comparison of prognostic scores in palliative care cancer populations. *Oncologist.* 2012;17(3):446-454.
17. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. a new method for detection of delirium. *Ann Intern Med.* 1990;113(12):941-948.

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ORIGINAL ARTICLE

Does a regional comprehensive palliative care program improve pain in outpatient cancer patients?

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Abstract
Context Pain is still a major problem for cancer patients, and the effect of a population-based approach on patients' experience of pain is not fully understood.
Aims The primary aim of this study was to clarify the changes in pain intensity in outpatients before and after a regional palliative care program. The secondary aim was to clarify the prevalence of patients who had unmet needs for pain treatment and to clarify the reasons for not wanting pain treatment.
Subjects and methods A regional palliative care program was implemented in four regions of Japan. A region-representative sample of metastatic/locally advanced cancer patients in outpatient settings took part in questionnaire surveys before and after the regional intervention. Responses were obtained from 859 from 1,880 and 857 from 2,123 in the preintervention and postintervention surveys, respectively.
Results After a regional palliative care program, neither worst, average, nor least pain levels in outpatients changed significantly. A total of 134 patients (16 %) reported that they needed more pain treatment. There were various reasons for not wanting pain treatment, namely, minimum interference with daily life, general nonpreference for medicines, longstanding symptoms before the diagnosis of cancer, concerns about tolerance and addiction, and experienced neuropsychiatric symptoms under current medications.
Conclusion The regional palliative care program failed to demonstrate improvement of the pain intensity of cancer outpatients. One possible interpretation is that they are less likely to be regarded as target populations and that the study

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population experienced generally well-controlled pain. Future study including patients with more severe pain is needed, but to improve pain levels of cancer outpatients, intensive, patient-directed intervention seems to be more promising than region-based intervention.

Keywords Palliative care · Community · Pain · Cancer · Barrier

Introduction

Pain is still one of the main symptoms of cancer patients and multiple surveys indicate that pain is frequently undertreated worldwide [1–4]. Pain is one of the major symptoms not only for terminally or physically ill patients but also for ambulatory cancer patients [5–11].

There are a variety of strategies to improve pain, including pharmacotherapy, nonpharmacological therapy, patient education, education for healthcare professionals, symptom screening, and feedback and audit [12–16]. One of them is a population-based approach, and several studies have investigated the effect of population-based intervention on pain of cancer patients [17, 18]. Pioneering work of a previous randomized controlled trial was to evaluate the effects of community intervention utilizing community leaders and educational strategies [17]. This 15-month program demonstrated not only a small decrease in pain prevalence and improvement in the pain management index but an increased pain intensity. The authors concluded that this intervention involving community leaders combined with educational programs has limited effects on pain intensity, and a more intensive intervention is necessary. Another study involving multimodal intervention included information and education [18]. Although the total amount of opioids increased 20 % in the control area vs. 210 % in the intervention area, the proportion of prescribing physicians remained constant (only a limited number of physicians actually prescribed a large amount of opioids). They concluded that this community-oriented intervention had a limited impact on cancer pain therapy at a population level.

On the other hand, a regional palliative care program is a way to comprehensively improve the quality of palliative care at a regional level, and a series of regional palliative care programs have been performed in Edmonton, Spain, Ontario, and Norway [19–24]. These studies examined the place of death, resource use, and quality of life; however, no studies investigated the effects of the program on patients' experience of pain. More recently, a region-based palliative care intervention program from Japan, the Outreach Palliative care Trial of Integrated Model (OPTIM) study, revealed that a regional palliative care program led to broad positive outcomes including patient- and family-reported quality of care, quality of life, place of death, and difficulties and knowledge of healthcare professionals [25–28]. This study adopted multiple end-points to obtain a comprehensive understanding of the intervention and included the pain intensity of patients recruited from a nearly representative sample of the regions.

Understanding the changes in pain intensity before and after a regional palliative care program could be useful to obtain insight into how to improve cancer pain at regional levels. The primary aim of this study was thus to clarify the changes in pain intensity before and after a regional palliative care program. Secondary aims were: (1) to clarify the prevalence of patients who had unmet needs regarding pain treatment, (2) to identify the determinants of unmet pain treatment needs, and (3) to clarify reasons for not wanting pain treatment after implementation of the regional palliative care program.

Subjects and methods

This is a descriptive observational study based on questionnaires administered to the patients and their families, before and after implementation of a regional palliative care program from Japan, the OPTIM study [25–28]. The questionnaire explores pain intensity, unmet needs for pain treatment, and potential determinants of unmet needs for pain treatment. The study methodology was described in detail in the methodology paper [26]. Ethical and scientific validity was confirmed by the institutional review board of this study and of all participating hospitals.

Overview of the OPTIM study [25]

This study was performed in four regions of Japan. We obtained preintervention data on outcomes before or in the early phase of the intervention period and postintervention data after or in the late phase of the intervention period. 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 quality of palliative care. Secondary end-points included patient-reported and bereaved family-reported quality of life, pain, caregiving burden, and knowledge, beliefs, and concern about palliative care. Intervention is a comprehensive program covering four areas: (1) to improve the knowledge and skills of palliative care (i.e., dissemination of manuals and assessment tools with interactive workshops about palliative care); (2) to increase the availability of specialized palliative care services for community patients (i.e., establishment of a new community palliative care team and outreach educational visits); (3) to coordinate community palliative care resources (i.e., regional palliative care centers, whole-region interdisciprenary conferences, patient-held records, and discharge-planning systems); and (4) to provide appropriate information about palliative care to the general public, patients, and families (i.e., dissemination of

leaflets, posters and DVDs, and workshops). We designed all interventions so they did not require a fundamental change in the healthcare system, that is, to optimize the existing healthcare resources within the region. All services were provided within national insurance, so that patients and families were economically freely accessible to all services. For outpatients, in addition to routine medical interventions from primary responsible physicians, patients received specialized palliative care services according to their demands. 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 family members confirmed that patients who died at home had preferred a 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 overall qualities of care were significantly better after intervention (effect size 0.14 and 0.23, respectively). Physician- and nurse-reported difficulties and knowledge of symptom control improved significantly. Accompanying qualitative analysis revealed that participants greatly emphasized improved communication and cooperation among regional healthcare professionals.

Subjects

Questionnaires were sent by mail to all patients who met the inclusion criteria. We intended to obtain a sample as representative of each region as possible. Data were collected in March/April 2008 as preintervention data and in November/December 2010 as postintervention data.

We obtained the participation of 23 of 34 hospitals in the study regions (8,964 of 11,033 beds, 81 %). Inclusion criteria were: (1) adults with 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 oncology or each specialty division; and (3) patients had been informed of the malignancy. We chose common primary tumor sites and did not include relatively uncommon cancers. Exclusion criteria included: (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) poor physical condition meaning that the patient was unable to complete the questionnaire.

Measurements

Pain intensity

Pain intensity of the patients is measured using the Japanese version of the Brief Pain Inventory, with a score given for the pain at its worst (0–10), at its best (0–10), and a score for the average pain felt (0–10) over the previous 24 h. The reliability and validity in Japanese populations has been established [29].

Unmet needs for pain treatment

In postintervention survey only, we asked patients who reported a score of one or more on the ten-point Likert-type scale of their worst pain about whether they needed more pain treatment (yes, no, or unsure). Patients who reported yes were defined as having unmet needs for pain treatment.

Potential determinants of unmet needs for pain treatment

As potential determinants of unmet needs for pain treatment, we used patient backgrounds, patient-reported quality of care, and patient-reported quality of life.

The quality of palliative care is measured using the Care Evaluation Scale, a well-validated and the most commonly used measurement tool to quantify the user-perceived quality of palliative care in Japan [30]. We excluded three subscales from the original scale, environment, cost, and availability, as they were unrelated to the intervention aim. Subscales used in this study thus included: (1) physical care provided by physicians, (2) physical care provided by nurses, (3) psycho-existential care, (4) help with decision making, and (5) coordination/consistency of care. Each item was graded on a six-point Likert-type scale from "1" improvement is highly necessary" to "6" improvement is not necessary at all, and the total score was calculated as the mean of subscale scores. Higher values indicated a lower perceived necessity for improvement.

Quality of life is measured using the patient version of the Good Death Inventory, a specific measure of the quality of life of Japanese patients with advanced cancer [31]. The full version of this scale was used, consisting of ten domains: (1) physical and psychological comfort, (2) living in one's favorite place, (3) maintaining hope and pleasure, (4) having a good relationship with medical staff, (5) not feeling a burden to others, (6) having a good relationship with the family, (7) being independent, (8) having environmental comfort, (9) being respected as an individual, and (10) a feeling of fulfillment at life's completion. Each item was graded on a seven-point Likert-type scale from "1" strongly disagree to "7": strongly agree, and the total score was calculated as the mean of subscale scores. Higher values indicated a higher perceived quality of life.

Reasons why the patients did not want pain treatment

For the patients who did not want more pain treatment, we asked about the reasons why they did not want pain treatment including minimum interference with daily life, general

nonpreference for medicines, longstanding symptoms before diagnosis of cancer, concerns about tolerance and addiction, experienced neuropsychiatric symptoms under current medications (e.g., somnolence, decreased concentration), experienced uncomfortable abdominal symptoms under current medications (e.g., nausea, constipation, appetite loss), and belief that analgesic medications is for dying patients. Patients were asked to choose all items applicable. The items were developed on the basis of existing literature [16, 32–36], discussion among the authors from multiple disciplines, and several focused groups and interviews of patients. We prepared "the others" item with free comments because there might be other reasons.

Use of palliative care service

To estimate the number of the patients who used palliative care services, we asked the patients whether they used any types of palliative care services (i.e., palliative care team, outpatient services, or palliative care units). This question was applied to only patients who reported slightly disagreed, disagreed, or strongly disagreed that they were free from physical distress (1 item of the Good Death Inventory) in postintervention survey.

Reference data

To interpret the findings of this study, we reported opioid consumption and pain relief of terminally ill cancer patients rated by the bereaved family members that were obtained as a part of secondary end-points.

Opioid consumption

We obtained two different values for opioid consumption using the administrative database of the prefectures every year during the study period (i.e., 2007, 2008, 2009, and 2010). One was total opioid consumption in the regions. The other was the total of oral morphine, oral oxycodone, transdermal fentanyl, and rectal morphine. These are all opioids covered by national health insurance for cancer pain, and none are licensed for use for noncancer pain; therefore, we assumed that the latter estimate would directly reflect the potential change in opioid consumption for cancer pain.

Pain relief of terminally ill cancer patients

A nearly representative sample of bereaved family members was obtained from homes, palliative care units, and hospitals throughout the region. Inclusion criteria were: (1) an adult family member of an adult patient with cancer who had died in a healthcare institution or at home; (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 3 or more days; and (4) the patient had been informed of the malignancy. Families were surveyed 6 to 12 months after the patients' death, and questionnaires were distributed in October 2008 and October 2011. Pain relief was measured using one item of the Good Death Inventory, "a patient is free from pain" on a seven-point Likert-type scale from "1": strongly disagree to "7": strongly agree [31].

Statistical analyses

To compare the changes in pain intensity before and after the interventions, the worst, average, and least pain intensity measured by the Brief Pain Inventory were compared using Student's *t* test. Differences in subject backgrounds, such as region, primary tumor sites, age, and sex, were adjusted. To investigate the changes in pain intensity with different patient characteristics, the worst pain was compared in the patients with a different performance status (0/1, 2, vs. 3/4), primary tumor site, age (<70 vs. 70 or older), and sex.

For ease of interpretation, we additionally calculated the percentages of pain distributions. Pain intensity was classified into four groups following the previous systematic review: no pain *0*, mild *1 to 4*, moderate *5 to 6*, severe *7 or more* [1].

We calculated the prevalence of patients' unmet needs by calculating the percentages with 95 % confidence intervals (95 % CI) of patients who reported that they needed more pain treatment out of all patients surveyed. Furthermore, to identify the determinants of unmet needs, we compared the patient backgrounds (age, gender, primary tumor sites, performance status, chemotherapy/radiotherapy), worst pain intensity, patient-reported quality of care, and patient-reported quality of life between patients with and without unmet needs. Comparisons were performed using Student's *t* test or the Chi-square test where appropriate. Logistic regression analysis was performed for variables with a significant difference ($P<0.05$).

We calculated the prevalence of reasons patients did not want pain treatment out of all patients with mild pain and moderate/severe pain. The responses for the others were few and not included in analyses.

Time trend in the changes of opioid consumptions per caner death within each region were tested by linear repeated measures regression analysis. Pain relief rated by the bereaved families was compared before and after with Student's *t* test. Differences in subject backgrounds were adjusted, and the weighted means of the death location according to census data from the four regions were used to adjust for differences in the proportions of the place of death of the patients sampled.

Table 1 Background characteristics

(1) Patient background			
Background characteristics	Before (n=859)	After (n=857)	P value
Region, % (n)			<0.0001
Tsuruoka	9.9 % (85)	19 % (166)	
Kashiwa	17 % (149)	22 % (192)	
Hamamatsu	39 % (337)	30 % (255)	
Nagasaki	34 % (288)	28 % (244)	
Mean age (years, standard deviation)	67 (11)	68 (11)	0.16
Sex			0.044
Male	55 % (476)	60 % (516)	
Female	45 % (383)	40 % (341)	
Primary tumor site			0.18
Lung	26 % (221)	26 % (223)	
Breast	17 % (148)	15 % (125)	
Colon, rectum	15 % (133)	14 % (124)	
Prostate, kidney, bladder	14 % (122)	15 % (132)	
Stomach, esophagus	11 % (92)	9.2 % (79)	
Liver, bile duct, pancreas	9.5 % (82)	11 % (95)	
Uterus, ovary	5.2 % (45)	7.8 % (67)	
Performance status			0.38
0	28 % (243)	32 % (271)	
1	43 % (371)	40 % (340)	
2	21 % (181)	19 % (166)	
3	4.3 % (37)	5.0 % (43)	
4	1.6 % (14)	1.5 % (13)	
Chemotherapy and/or radiotherapy			0.84
Receiving	58 % (498)	56 % (484)	
Not receiving	40 % (343)	40 % (340)	
(2) Background of bereaved families			
Background characteristics	Before (n=1,110)	After (n=1,137)	P value
Region, % (n)			0.024
Tsuruoka	17 % (184)	18 % (204)	
Kashiwa	19 % (211)	14 % (162)	
Hamamatsu	39 % (432)	40 % (458)	
Nagasaki	25 % (283)	28 % (313)	
Patient age, years			<0.0001
20–29	0·2 % (2)	0 % (0)	
30–39	0·5 % (5)	0·7 % (8)	
40–49	2·1 % (23)	1·8 % (21)	
50–59	11 % (122)	7·1 % (81)	
60–69	23 % (251)	21 % (238)	
70–79	36 % (403)	33 % (380)	
80–89	23 % (259)	29 % (326)	
90–	3.9 % (43)	6.2 % (71)	
Patient sex			0.47
Male	62 % (689)	61 % (688)	
Female	36 % (402)	38 % (428)	
Primary tumor site			0.88
Lung	27 % (298)	26 % (294)	
Stomach, esophagus	20 % (218)	18 % (205)	

Table 1 (continued)

Pancreas, bile duct	14 % (154)	16 % (179)	
Liver	11 % (119)	11 % (120)	
Colon, rectum	10 % (111)	11 % (120)	
Prostate, kidney, bladder	6.4 % (71)	6.9 % (78)	
Breast	4.0 % (44)	4.2 % (48)	
Uterus, ovary	3.7 % (41)	3.3 % (37)	
Family member age, years (%)			0.0062
20–29	0.8 % (9)	0.5 % (6)	
30–39	3.4 % (38)	3.0 % (34)	
40–49	13 % (141)	11 % (127)	
50–59	28 % (306)	24 % (273)	
60–69	29 % (317)	31 % (354)	
70–79	21 % (231)	23 % (256)	
80–89	4.9 % (54)	6.4 % (73)	
90–	0.3 % (3)	0.4 % (4)	
Family member sex			0.11
Male	31 % (341)	28 % (313)	
Female	68 % (753)	71 % (802)	
Relationship to patient			0.79
Husband/wife	53 % (583)	52 % (594)	
Child of patient	39 % (431)	39 % (449)	
Sibling	4.1 % (45)	3.3 % (37)	
Parent of patient	1.4 % (15)	1.7 % (19)	
Others	2.4 % (27)	2.1 % (24)	
Death location			<0.0001
Hospital	72 % (797)	59 % (668)	
Palliative care unit	21 % (236)	22 % (248)	
Home	6.9 % (77)	19 % (221)	
Stay with patients during the last week			0.15
Every day	72 % (795)	73 % (833)	
4–6 days	11 % (123)	12 % (134)	
1–3 days	9.7 % (108)	7.9 % (90)	
None	6.4 % (71)	5.1 % (58)	

The percentages do not add up 100 % due to missing values. Chi-square test or Wilcoxon's rank–sum test

All analyses were performed with the SAS software package, version 9.3 (SAS Institute, Cary, NC, USA).

Results

We obtained a total of 859 (response rate 58 %) and 857 (response rate 57 %) analyzable responses from 1,488 and 1,501 patients in the preintervention and postintervention surveys, respectively. We also obtained a total of 1,110 (response rate 69 %) and 1,137 (response rate 66 %) analyzable responses from 1,658 and 1,728 families, respectively. Background characteristics are summarized in Table 1. Among 118 patients who slightly disagreed, disagreed, or strongly disagreed that they were free from physical distress from 1,137 patients in postintervention survey, 20 patients reported they received specialized palliative care service, 57 patients did not, and the remaining 41 patients reported unsure.

Change in pain intensity

None of the worst, average, and least pain changed significantly after the regional intervention program (Table 2). No significant changes were observed in all subgroups of patients a with performance status of 0/1, 2, 3/4 (Table 2). Subgroup analyses of the primary tumor site, age, and sex revealed that there were no significant changes in pain intensity between the observation periods (data not shown).

On the other hand, pain relief of terminally ill cancer patients rated by bereaved families significantly improved after the intervention (Table 2).

On the basis of the worst pain reported, the percentages of patients who reported moderate to severe pain was 16 % (95 % CI 14–19) in the preintervention survey and 17 % (95 % CI 13–18) in the postintervention survey (Table 3). A total of 488 (57 %; 95 % CI 54–60) of 857 patients in the postintervention survey reported a pain intensity of 1 or more.

Unmet needs for pain treatment

In total, 134 patients agreed that they needed more pain treatment. This corresponds to 16 % of all 857 patients surveyed (95 % CI, 13–18), and 27 % of 488 patients with a pain intensity of 1 or more (95 % CI 24–32). The prevalence of patients with unmet needs increased according to the pain intensity (Fig. 1). While 23 % of patients needed pain

Table 2 Changes in pain intensity of outpatients and pain relief of terminally ill cancer patients rated by the bereaved family members

Items	Before	After	*P* value	Adjusted *P*
Outpatients				
Worst pain, mean (standard deviations)	1.92 (2.49)	1.93 (2.43)	0.97	0.62
Average pain	1.50 (1.97)	1.48 (1.89)	0.85	0.80
Least pain	0.94 (1.48)	0.96 (1.48)	0.73	0.62
Subgroups of outpatients with different performance status				
0 or 1	1.47 (2.11)	1.53 (2.12)	0.61	0.31
2	2.80 (2.83)	2.68 (2.57)	0.71	0.80
3 or 4	4.18 (3.26)	4.07 (3.38)	0.87	0.85
Terminally ill patients (proxy by bereaved family)				
Pain relief*	4.30 (1.75)	4.55 (1.64)	0.001	0.002

*Rated based on one item of the Good Death Inventory: "a patient is free from pain" on a seven-point Likert-type scale from "1" strongly disagree to "7" strongly agree

treatment in those with mild pain, 49 % did in those with severe pain.

Determinants of unmet needs for pain treatment

The patients with a younger age, better performance status, receiving chemotherapy/radiotherapy, more severe pain, lower perceived quality of care, and perceived lower quality of life were significantly more likely to have unmet needs for pain treatment (Table 4). Multivariate analyses identified severe pain and a lower quality of life as independent determinants of unmet needs for pain treatment. This model explained the variance of 0.12 (R square of Nagelkerke).

Reasons for not wanting pain treatment

Reasons for not wanting pain treatment reported by the patients markedly differed between those with mild and moderate/severe pain (Fig. 2). Minimum interference with daily life was the most common reason in patients with mild pain (74 %) and also those with moderate/severe pain (41 %). In both pain groups, general nonpreference for medicines was listed as a reason in about 30 %, and longstanding symptoms before diagnosis of cancer was listed in about 20 %. Patients with moderate/severe pain listed concerns about tolerance and addiction most frequently (38 %), followed by the experience of neuropsychiatric and abdominal symptoms under the current medications and the belief that analgesic medication is for dying patients (15 to 18 %).

Opioid consumption

Total opioid consumption significantly increased from 64,035 g for four regions in 2007 to 103,542 g in 2010 (P= 0.034, adjusted for cancer death; Fig. 3). Opioid consumption of oral morphine, oxycodone, and transdermal fentanyl significantly increased from 43,839 g for four regions in 2007 to 68,517 g in 2010 (P=0.0044, adjusted for cancer death).

Discussion

This is, to our best knowledge, the first analyses of changes in pain intensity in outpatients before and after a comprehensive region-based palliative care program using a nearly regionally representative sample.

The most important finding is that this regional palliative care intervention program demonstrated no measurable effects on pain intensity in advanced cancer patients receiving outpatient treatment, despite significant increase in opioid

Table 3 Changes in distributions of worst pain intensity

	Before (n=859)	Percentage	95 % CI	After (n=857)	Percentage	95 % CI
Worst pain						
None	348	42 %	39, 46	343	41 %	38, 45
Mild	335	41 %	37, 44	355	40 %	39, 46
Moderate	73	8.9 %	7.0, 11	70	8.4 %	7.0, 11
Severe	68	8.3 %	7.0, 10	63	7.6 %	6.0, 10
Missing	35	–	–	26	–	–

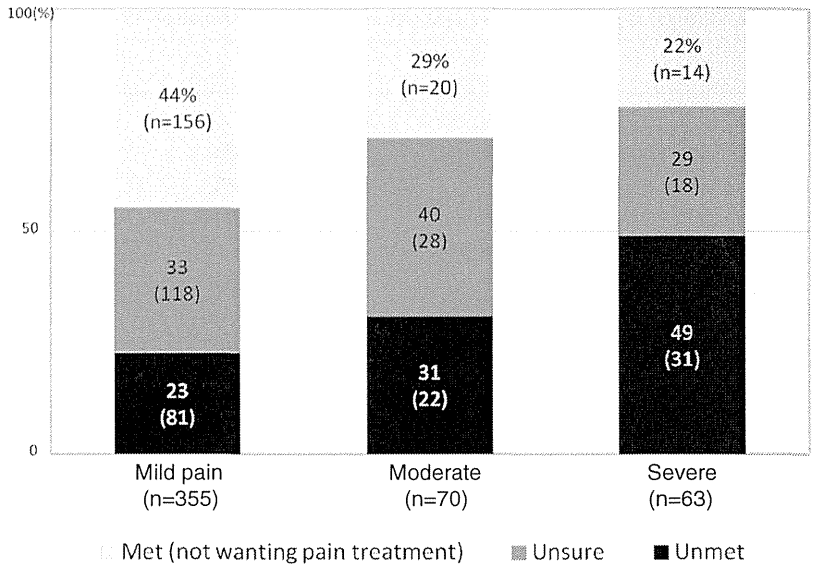

Fig. 1 Need for pain treatment

consumption and improvements in pain relief of terminally ill cancer patients rated by families. This is consistent with the total population and all subgroups with a poor performance status. This seems to contradict with other favorite outcomes observed in this study including improved physicians' and nurses' knowledge and difficulties regarding palliative care (including pain management) and improved patient-reported quality of palliative care (i.e., patients reported that physicians were significantly more likely to deal promptly with discomforting symptoms and that nurses promptly dealt with the patients' needs) [25].

There are many interpretations of this result. The first interpretation is that the comprehensive regional palliative care intervention actually contributed to improvement in

Table 4 Determinants of unmet needs for pain treatment

Potential determinants	Univariate analyses			Multivariate analyses		
	Patients with unmet needs (n=134)	Patients without unmet needs (n=354)	P value	Odds ratio	95 % Confidence intervals	P value
Age (mean, S.D.)	66 (11)	69 (11)	0.012			
Sex						
Male	60 % (80)	60 % (213)	0.99			
Female	40 % (54)	40 % (141)				
Primary tumor site						
Lung	22 % (29)	27 % (95)	0.011			
Breast	17 % (23)	17 % (59)				
Colon, rectum	22 % (30)	12 % (42)				
Prostate, kidney, bladder	10 % (14)	16 % (57)				
Stomach, esophagus	15 % (20)	8.5 % (30)				
Liver, bile duct, pancreas	7.5 % (10)	12 % (43)				
Uterus, ovary	6.0 % (8)	7.3 % (26)				
Performance status	1.5 % (0.94)	1.2 % (0.87)	0.001			
Chemotherapy/radiotherapy	68 % (91)	56 % (197)	0.046			
Worst pain (0–10)	4.1 (2.6)	2.9 (2.2)	<0.001	1.18	1.07–1.29	<0.001
Quality of care*	4.3 (0.95)	4.5 (0.95)	0.23			
Quality of life**	5.0 (0.82)	5.3 (0.82)	<0.001	0.72	0.56–0.94	0.015

*Measured using the Care Evaluation Scale, ranging from 1 to 6, with a higher score indicating a lower perceived necessity for improvement

**Measured using the Good Death Inventory, ranging from 1 to 7, with a higher score indicating a higher perceived quality of life

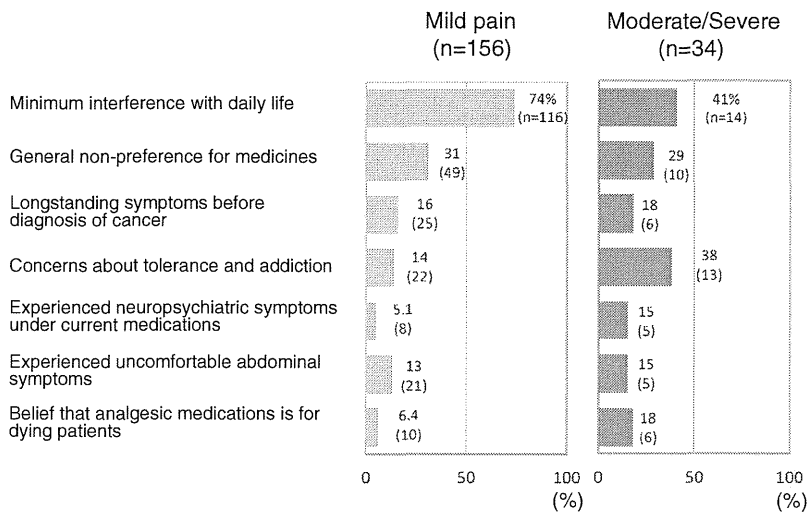

Fig. 2 Reasons for not wanting pain treatment

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

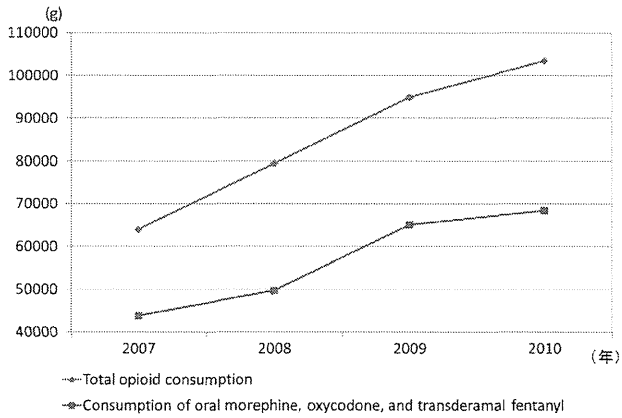

Fig. 3 Changes in opioid consumption

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.

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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

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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?

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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

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