

ん対策における管理評価指標群の策定とその計測システムの確立に関する研究班」において疼痛の quality indicator も開発されて実測されたものの、実測にかかる時間とエビデンスの希薄さから十分なものとは言えなかった。したがって、がん疼痛治療の quality indicator の実測を行うとするならば、開発を再度試みる必要がある。オピオイド消費量については、本研究で用いた方法でよいのかについてはゴールドスタンダードとの比較が必要である。

以上の研究結果があきらかになるまでは、オピオイド消費量をもってして施設のがん疼痛の質の評価とすることは保留する必要がある。少なくとも、施設間の比較に用いるべきではない。施設単位の疼痛治療の質の評価指標、特に施設間の比較は国際的にみても確立した方法がないことを踏まえ、「いま利用可能な指標」を参考として行いながらも、並行して、より妥当性・信頼性のある指標の開発を地道に行うことが必要である。

資料1 各施設に配布したオピオイド消費量のフォードバック用紙

がん診療連携拠点病院におけるオピオイドの消費量に関する調査結果

方法

2009年から2013年について、各施設から都道府県に提出された「オピオイド払い出し量」を施設からの転記によって求め、厚生労働省から提出されている「院内がん登録患者総数」「年間新入院がん患者数」「年間院内死亡がん患者数」「年間外来がん患者のべ数」を取得した。フェンタニル注射については、手術麻酔で多く使用されていることが想定され今回の集計からは除外した（モルヒネ、オキシコドン、コデイン、フェンタニル貼付剤を対象とした）。オピオイド等価換算は通常の臨床用量に基づいて換算した。院内がん登録患者総数、年間新入院がん患者数、年間外来がん患者数、院内がん死亡者数については、2013年分はまだ集計されていないため、2009年から2012年の4年分を集計した。

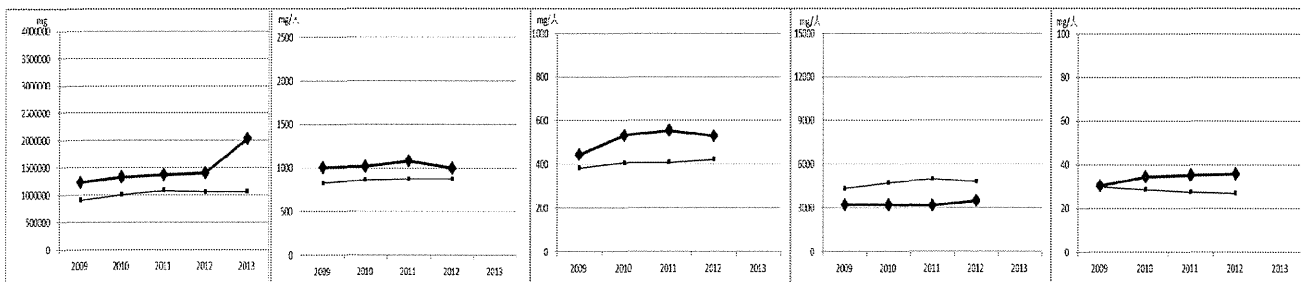
オピオイド払い出し量合計(オピオイド量合計)、オピオイド払い出し量合計/院内がん登録患者総数(オピオイド量/がん登録数)、オピオイド払い出し量合計/年間新入院がん患者数(オピオイド量/新入院がん患者数)、オピオイド払い出し量合計/がん死亡者数(オピオイド量/がん死亡数)、オピオイド払い出し量合計/年間外来がん患者のべ数(オピオイド量/外来がん患者数)を算出して、グラフ化した。

平成25年8月1日時点でがん診療連携拠点病院に指定されている397施設に調査票を送付した。308施設(77%)から返送があり、このうち4件は回答不可であった。解析対象施設は304施設(76%)であった。

結果 ○○○○病院

1 オピオイド使用量の推移

オピオイド量合計 オピオイド量/がん登録数 オピオイド量/新入院がん患者数 オピオイド量/がん死亡数 オピオイド量/外来がん患者数



*全国中央値を細線、各施設の値を太線で表した

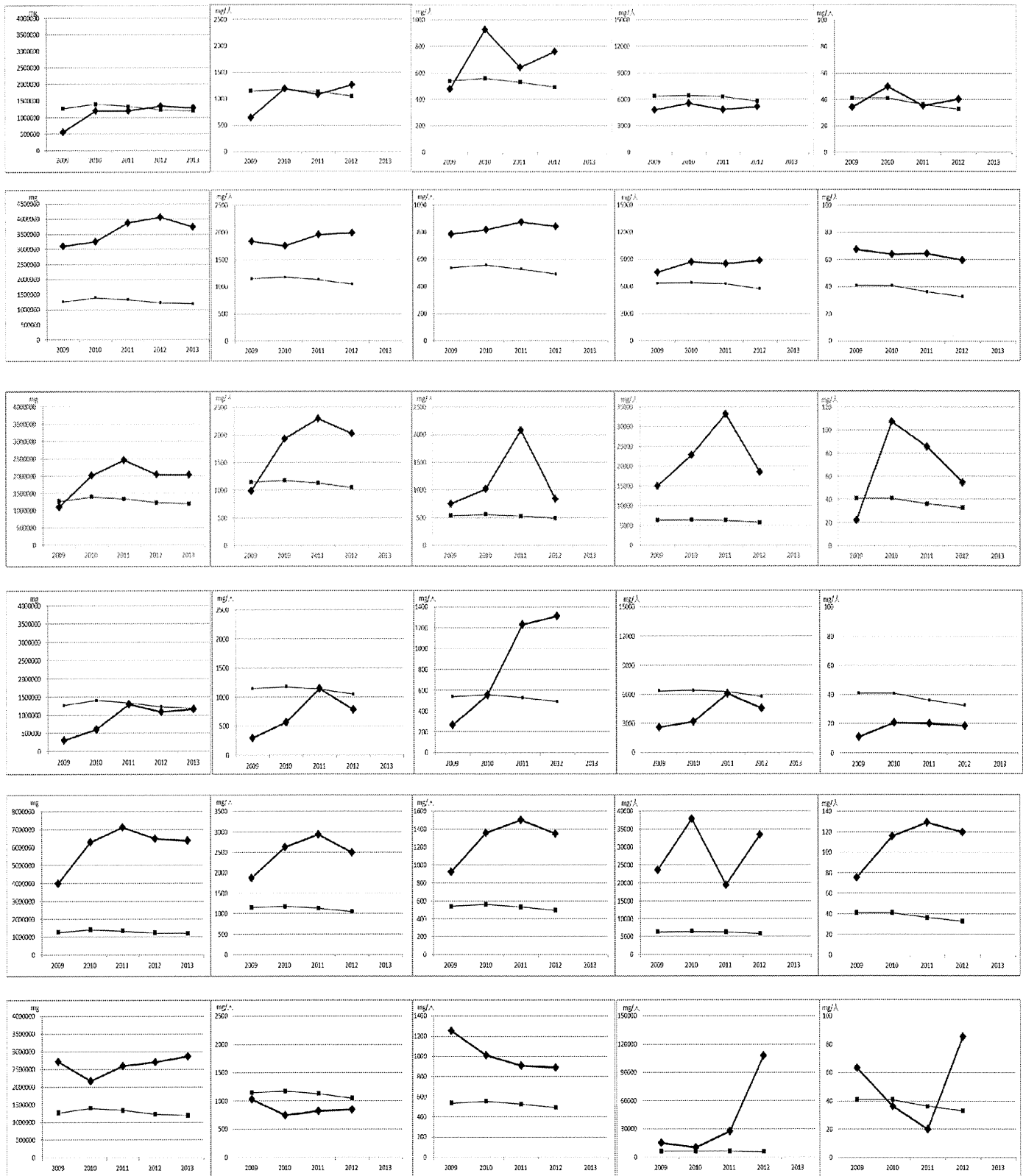
2 オピオイド使用量の調査施設内の順位 (304施設中上位から数えて何番目か)

オピオイド量合計					オピオイド量/がん登録数				オピオイド量/新入院がん患者数				オピオイド量/がん死亡数				オピオイド量/外来がん患者数			
'09	'10	'11	'12	'13	'09	'10	'11	'12	'09	'10	'11	'12	'09	'10	'11	'12	'09	'10	'11	'12
107	105	101	97	62	109	105	102	124	112	89	89	99	195	226	240	224	136	128	116	113

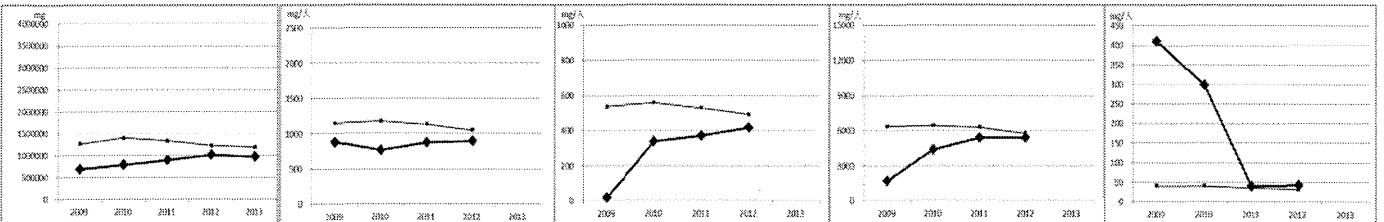
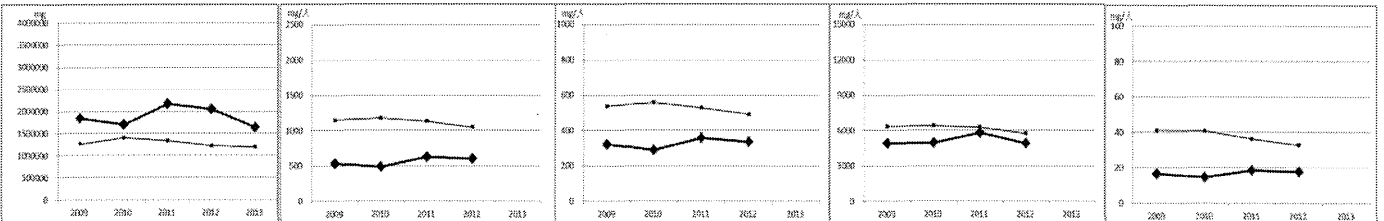
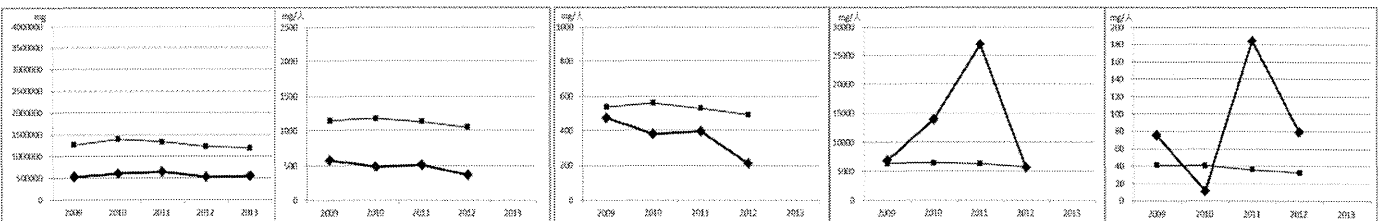
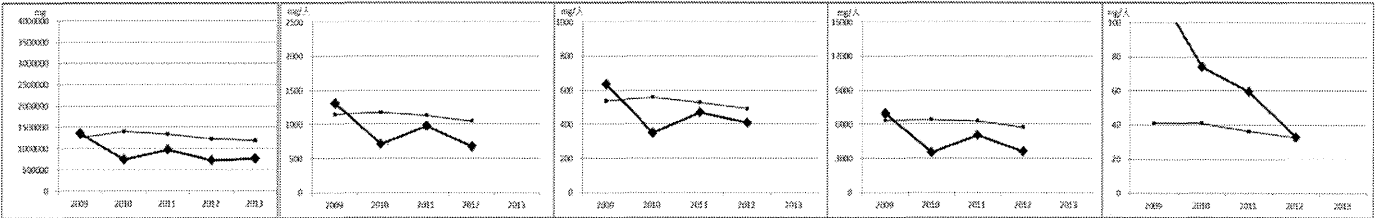
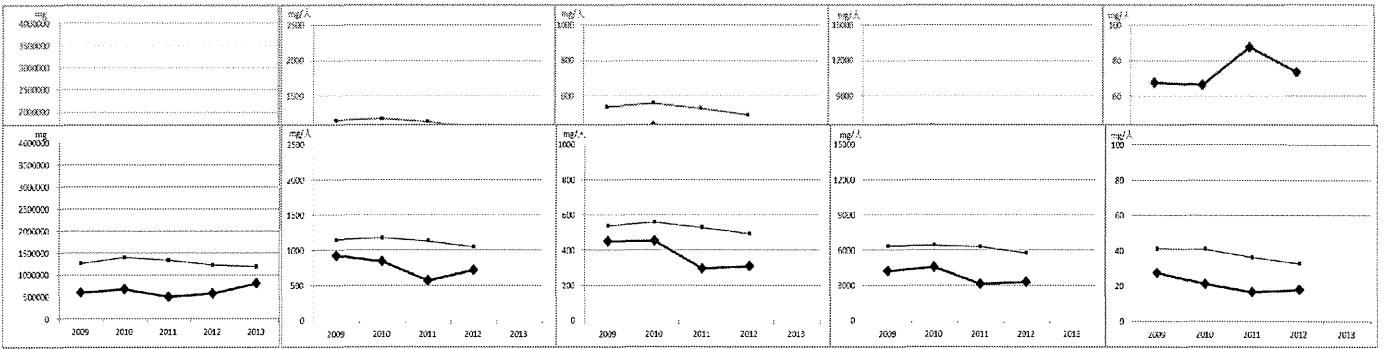
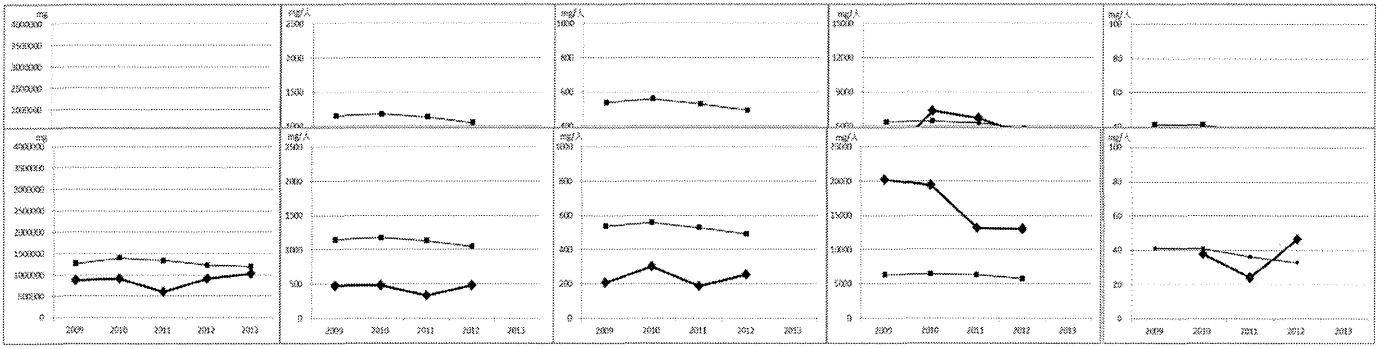
(以上)

資料 2 多い施設・少ない施設のオピオイド消費量

a. 多い施設の例



b. 少ない施設の例



Ⅱ. 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
該当なし							

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
Hamano J, Kizawa Y, Maeno T, Nagaoka H, Shima Y, Maeno T.	Prospective clarification of the utility of the palliative prognostic index for patients with advanced cancer in the home care setting..	Am J Hosp Palliat Care.	31(8)	820-824	2014
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
Morita T, Miyashita M, Yamagishi A, Akiyama M, Akizuki N, Hirai K, Imura C, Kato M, Kizawa Y, Shirahige Y, Yamaguchi T, Eguchi K.	Effects of a programme of interventions on regional comprehensive palliative care for patients with cancer: a mixed-methods study.	Lancet Oncol	14(7)	638-646	2013

(註) 研究責任者、研究責任者の平成25～26年度の研究発表については、総合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。

Ⅲ. 研究成果の刊行物・別刷

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

American Journal of Hospice & Palliative Medicine®
2014, Vol. 31(8) 820-824
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sagepub.com/journalsPermissions.nav
DOI: 10.1177/1049909113504982
ajhpm.sagepub.com



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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 care¹ 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 studies¹⁴ 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 \pm SD)	75.6 \pm 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	\geq 3 weeks' survival	Total
$PPI \geq 6$	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	\geq 6 weeks' survival	Total
$PPI \geq 4$	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 al¹³ 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 al¹⁶ 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 al¹³ and Maltoni et al¹⁶ 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 while the median duration of survival was 40 days in our study, Morita et al¹³ reported 27 days and Maltoni et al¹⁶ 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 al¹³ and Maltoni et al¹⁶ 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 al¹³ reported prevalence of 38%, 35.4%, and 18% and Maltoni et al¹⁶ 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 re-evaluate this question using a larger sample size from this patient population before forming a definitive conclusion, because a previous study¹¹ 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.

Acknowledgment

All authors acknowledge Tatsuya Morita.

Declaration of Conflicting Interests

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

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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

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Received: 30 January 2014 / Accepted: 25 March 2014 / Published online: 5 April 2014
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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 interdisciplinary 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 cancer 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 (<i>n</i> =859)	After (<i>n</i> =857)	<i>P</i> value
<i>Region, % (n)</i>			<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
<i>Sex</i>			0.044
Male	55 % (476)	60 % (516)	
Female	45 % (383)	40 % (341)	
<i>Primary tumor site</i>			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)	
<i>Performance status</i>			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)	
<i>Chemotherapy and/or radiotherapy</i>			0.84
Receiving	58 % (498)	56 % (484)	
Not receiving	40 % (343)	40 % (340)	
(2) Background of bereaved families			
Background characteristics	Before (<i>n</i> =1,110)	After (<i>n</i> =1,137)	<i>P</i> value
<i>Region, % (n)</i>			0.024
Tsuruoka	17 % (184)	18 % (204)	
Kashiwa	19 % (211)	14 % (162)	
Hamamatsu	39 % (432)	40 % (458)	
Nagasaki	25 % (283)	28 % (313)	
<i>Patient age, years</i>			<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)	
<i>Patient sex</i>			0.47
Male	62 % (689)	61 % (688)	
Female	36 % (402)	38 % (428)	
<i>Primary tumor site</i>			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)	
<i>Family member age, years (%)</i>			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)	
<i>Family member sex</i>			0.11
Male	31 % (341)	28 % (313)	
Female	68 % (753)	71 % (802)	
<i>Relationship to patient</i>			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)	
<i>Death location</i>			<0.0001
Hospital	72 % (797)	59 % (668)	
Palliative care unit	21 % (236)	22 % (248)	
Home	6.9 % (77)	19 % (221)	
<i>Stay with patients during the last week</i>			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
<i>Outpatients</i>				
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
<i>Subgroups of outpatients with different performance status</i>				
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
<i>Terminally ill patients (proxy by bereaved family)</i>				
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).

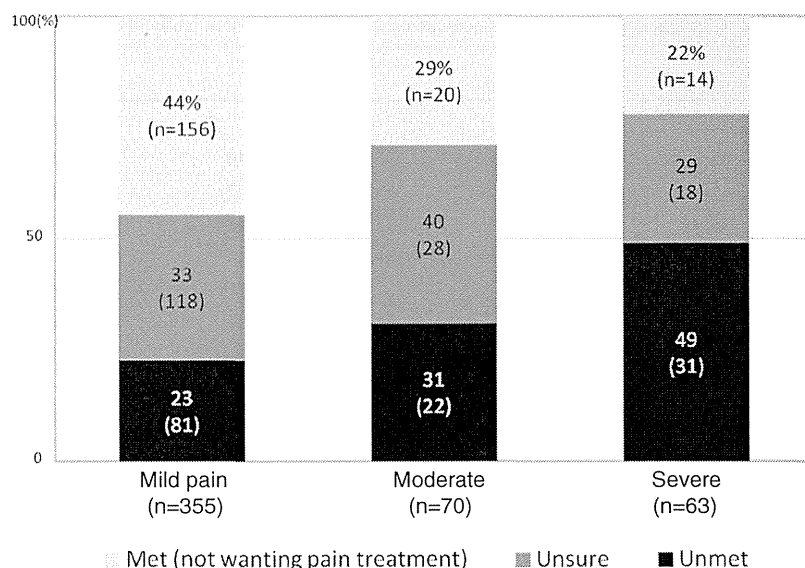
Discussion

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
<i>Worst pain</i>						
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			
<i>Sex</i>						
Male	60 % (80)	60 % (213)	0.99			
Female	40 % (54)	40 % (141)				
<i>Primary tumor site</i>						
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