参加地域：豊見城中央病院（沖縄県）

沖縄県地域中核一般病院（がん拠点病院以外）における疼痛スクリーニング

社会医療法人友愛会南部病院・豊見城中央病院
緩和ケアチーム
笹良剛史　朝川恵利　高見洋二

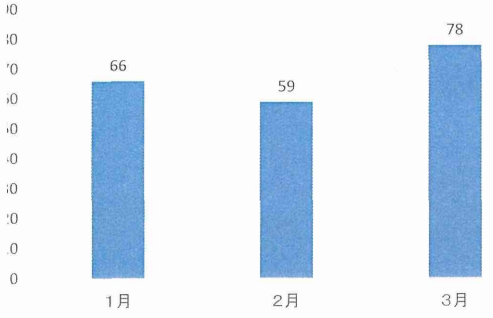
H27年的場班会議

背景

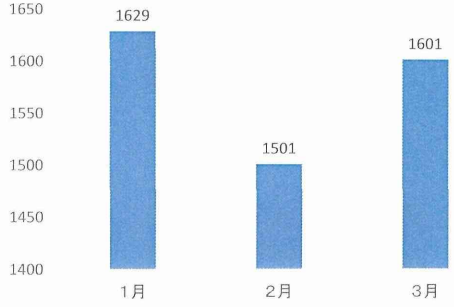
- 当院は沖縄県南部の豊見城市に位置する地域医療支援、研修指定機能をもつ一般総合病院、
  - がんの診断、手術、化学療法は行っている
  - 放射線施設はなく。がん拠点病院ではない
- 緩和ケアチーム加算なし
  - 専従のがん疼痛認定看護師が配置されているが、身体緩和医は兼任、4月より常勤の精神科医着任、緩和ケアチームに参加
- 友愛会南部病院（糸満市）を核とする緩和トライアングル
  - 緩和ケア病棟と訪問看護ステーション、訪問診療部、包括支援センターが連携
  - 豊見城中央病院の後方支援機能

豊見城中央病院：ベッド数　３７５床
H26年間総退院患者数：１３４８７人（前年度１３６２９人）
H26年間がん患者退院数：１０５９人（前年度９７９人）
H26がん患者退院比率：７．２％

H27. 1月~3月 : 入院がん患者数



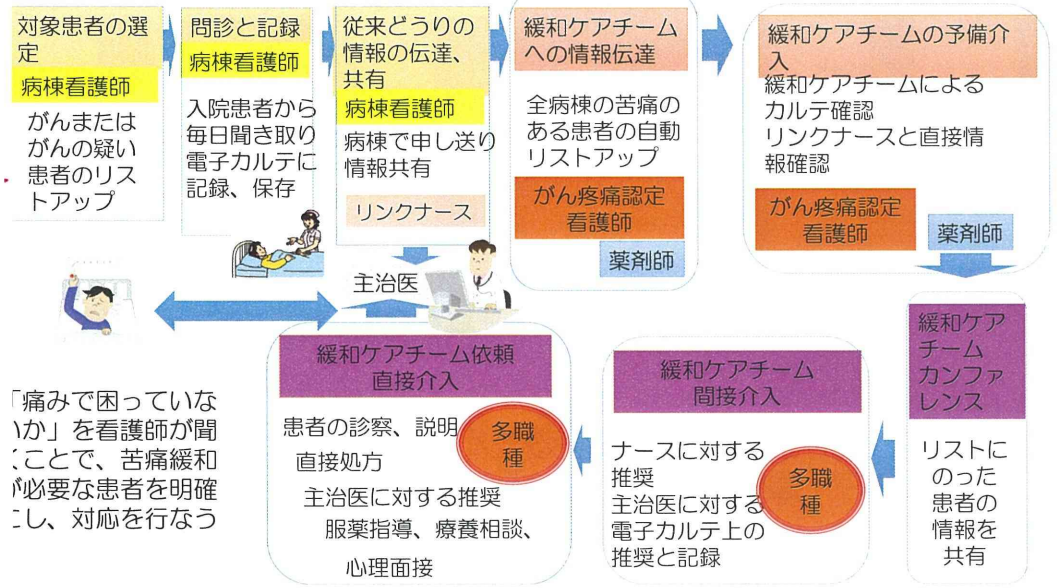
H27.1月~3月 : 外来がん患者数



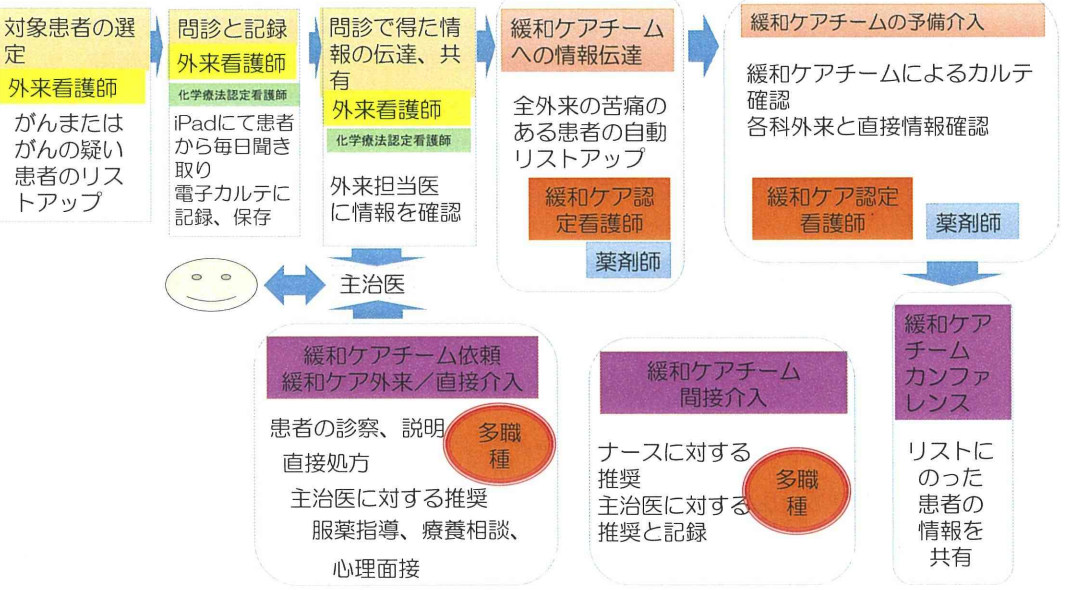
友愛会豊見城中央病院、南部病院における苦痛スクリーニングの経緯

1. 平成２０年６月に緩和ケアチームを発足させ、活動を開始した。
2. 平成２１年１０月より、名古屋緩和カンファレンス（名古屋パック）における方法を参考に、入院がん性疼痛患者に対する除痛率調査を豊見城中央病院、南部病院にて開始。
3. 平成25年度よりSPARKSをもとに情報システム課による問診スクリーニングと除痛率算出のシステム構築し導入
4. 一般病棟看護師対象に基本的な知識の評価の現状把握：疼痛評価方法、WHO方式に関する認識調査
5. 一般病棟看護師への疼痛評価、治療法に関する病棟ごと教育講座の実施
6. 疼痛スクリーニングを日常業務化する病棟を少しずつ拡大
7. 緩和ケアチームカンファレンス時に除痛率報告
   1. 「チームに依頼されていないが痛みで困っている患者」の拾い上げ
   2. 病棟担当薬剤師や認定看護師の介入に利用

入院患者の苦痛スクリーニングと運用フロー

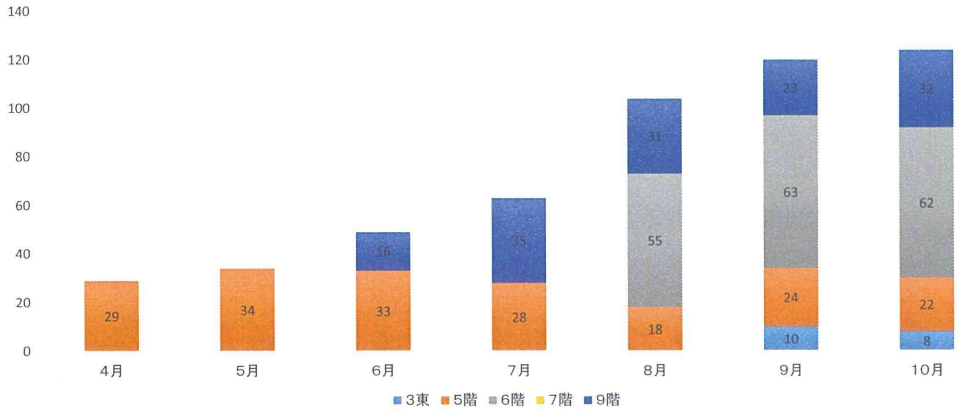


外来患者の苦痛スクリーニングと運用フロー（案）

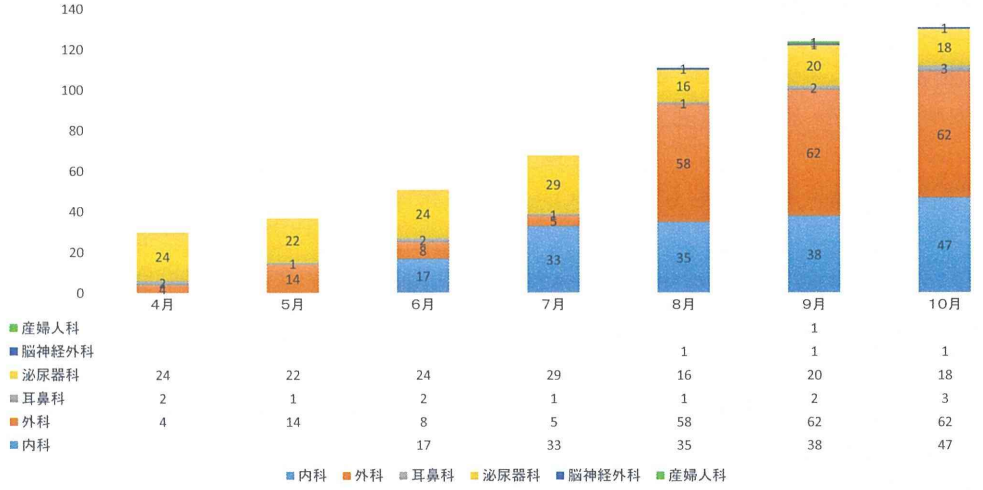


2014年4月～10月

病棟別疼痛スクリーニング実施患者数



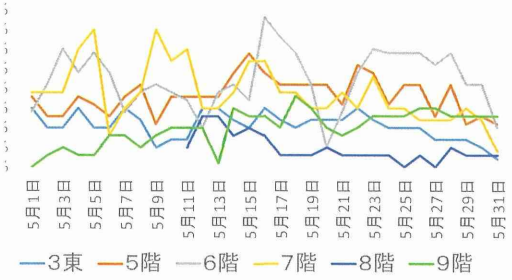
診療科別疼痛スクリーニング実施患者数



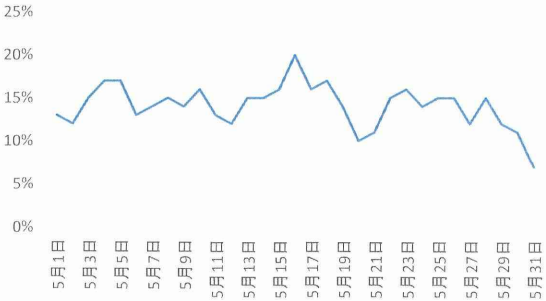
疼痛スクリーニングシート運用の流れ

スクリーニング開始時期	病棟	ベッド数
H26.4月~試験運用開始	5階：泌尿器科、小児科、耳鼻科	38床
H26.6月~	9階：消化器内科	40床
H26.7月~	6階：外科、婦人科	42床
H26.8月~	3東：呼吸器内科、神経内科	41床
H26.11月~	7階：全個室、混合病棟	26床
H27.5月~	8階：産科、整形外科、形成外科	40床
H27.6月~	3北：腎臓内科、膠原病、リウマチ科	34床
H27.7月	3新：整形外科	40床
H27.8月	3西：循環器内科	41床

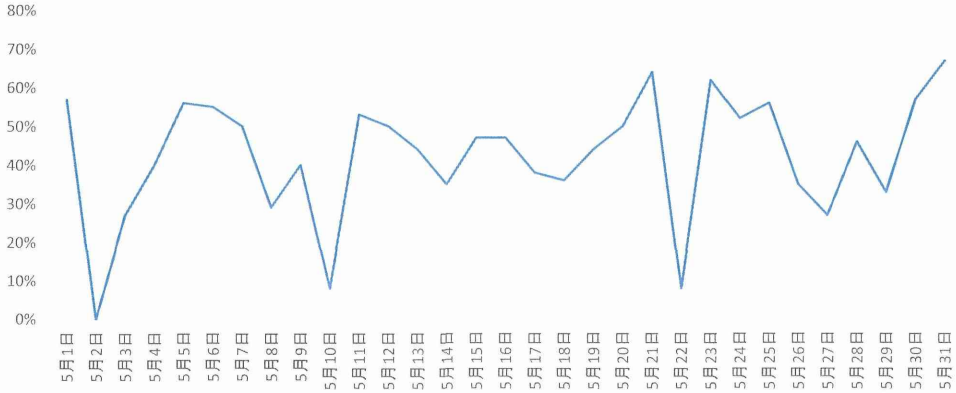
6病棟（227床）スクリーニング使用率比較



375床のうち227床（6病棟）スクリーニング使用率



6病棟除痛率



看護師からみた問題点

- 教育、導入
  - シート開始直前アンケートからWHO方式疼痛治療法や疼痛評価法、STAS-Jについて言葉だけ知っている、全く知らないと70%が答えている→このことから教育内容など十分検討し計画する必要があった
  - これまで勉強会など行なってきていなかった事もあり、開始が早急だったと思われます
  - 教育の継続が必要（シートの結果から症例検討など）
- 対象患者の選択、日常業務としての問題
  - がんと予測されるが高齢で確定診断を希望されない方の評価はどうするか病棟で混乱
  - 以前がんと診断されているが、根治されているであろう患者さんは対象となるのか、業務負担感
- 医師へのフィードバックや多職種での共有に生かされていない
  - 医師に対する院内での啓発、フィードバックシステム
  - 医師への説明
- システムの問題
  - アルゴリズムに不備があり、除痛率が0—100%
  - 記録として見づらいため修正が必要

これからの予定

- 全病棟看護師への疼痛緩和教育講座実施とスクリーニング周知徹底
- 電子カルテにおけるスクリーニング業務および集計システムの完成
- 病院全体、看護部、医局会、診療録委員会と疼痛スクリーニング日常業務化の周知とコンセンサスの確定
- 主治医、病棟看護スタッフへの迅速なフィードバックの実施
- 患者・家族への疼痛スクリーニングの広報、周知
- 対応できる緩和ケアチーム力の向上　勉強会の定期開催開始
- 薬剤師を主体とするSCOPE回診の導入
- 南部病院の緩和ケア病棟以外の病棟への導入
- 外来通院患者に対するipad導入　病院に起案承認済み
- がん以外の疼痛スクリーニングに利用：課題
- 他の病院、診療所、在宅とのスクリーニング方法、データーの共有化も課題

苦痛のスクリーンングについて
がん診療担当医へのお願い

全がん患者に対する

苦痛の日常的スクリーニングが必須になりました。

外来や病棟で問診票や看護師による聞き取りを行っています

スクリーニングで得られた苦痛の評価のカルテ記録をご確認ください。

その上で、苦痛の緩和のための

主治医で可能な指示、処方と

相談室や緩和ケアチーム、専門家へのサポート依頼などの

ご協力お願いします。

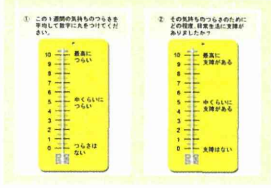
緩和ケアチーム：▪▪▪▪、相談室　▪▪▪にご連絡を

おしえてください
あなたの痛みとつらさ
困ったこと　気がかりなこと

- 外来や病棟で
- 痛みなどの体の症状、気持ちのつらさなど、こまったことについて問診を行います。
- iPadや質問票を用いてあなたの困ったことを把握します。
- 痛みや辛さの程度は数字や図を使って評価します

その上で

- すぐに解決できる困った問題は主治医とすばやく相談
- じっくり皆んなで相談したほうがいいことは、チーム医療で解決します
- 看護師さんや担当係による問診にご協力お願いします



まとめ

- 沖縄県ではがん拠点病院、一般病院において疼痛スクリーニングの日常化を目指している
- システム化、教育　医療者への周知、等の改善要す
- 医師の意識改革はこれからです。

- 「苦痛にしっかり向き合い、早くから緩和できる地域、病院」にむけ、ご指導お願いします

入院患者の疼痛スクリーニングがオピオイド処方量に及ぼす影響

川平茜[1] 福地愛[1] 伊波友理華[1] 笹良剛史[2] 余語久則[3]
朝川恵利[4] 玉寄菜穂[5] 上運天小百合[5] 橋本孝夫[1]

1)豊見城中央病院　薬剤科、2)友愛会南部病院　緩和ケア内科
3)豊見城中央病院　麻酔科・緩和ケアチーム
4)県立宮古病院　認定看護師、5)豊見城中央病院　緩和ケアチーム

はじめに

がん診療連携拠点病院において、疼痛スクリーニングが義務化され、一部の病院では運用され始めているが、その効果については明らかではない。

当院緩和ケアチームでは、がん患者に対する疼痛スクリーニングを平成26年5月から導入を開始して、患者の苦痛を評価し、緩和ケア活動に活かしてきた。

当院概要

所在地：沖縄県豊見城市
許可病床数：376床
診療科目：37診療科
常勤医師：110名
平均在院日数：10日
1日平均外来患者数：878名
平成26年度実績

月間平均がん入院患者数128名、
緩和ケア病棟なし

目　的

今回、更なる疼痛スクリーニングの有効活用に繋げるため、拠点病院ではない地域の急性期病院である当院でのスクリーニング運用状況を把握し、オピオイド消費量と除痛率の変化を中心に後方視的に調査した。

疼痛スクリーニングシート

入院がん患者全員について、病棟看護師が基本的に毎日入力

痛みの程度は「軽度」「中程度」「高度」かNRS 1～10 のどちらかで入力できる。

すべての項目をクリックと選択のみで入力可能

※青森県立中央病院の Special Project for Awareness and Relief of Cancer Symptoms (SPARCS) に準拠

疼痛スクリーニングシートの集計表

疼痛スクリーニングシートに入力されたデータは自動的に集計され一覧となって閲覧可能

PMI: 1 強い痛み（NRS 7-10）に弱オピオイド、中等度の痛み（NRS 4-6）に非オピオイド、弱い痛み（NRS 1-3）が未治療
PMI: 2 強い痛みに非オピオイド、中等度の痛みが未治療
PMI: 3 強い痛みが未治療

除痛率

	痛みで困り･出来ない事（＋）	痛みで困り･出来ない事（－）
痛みの治療（＋）	①	②
痛みの治療（－）	③	除外

基本的に、痛みがあっても治療をしていない人は困っている。

$$除痛率(\%) = \frac{②}{①+②+③}$$

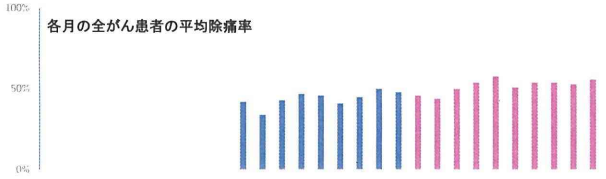
除痛率：「痛みでできないことや困っていることがある」患者と「鎮痛薬を使用している」患者を分母として、その中で「鎮痛薬を使用していてできないことや困っていることはない」患者を分子として計算した割合

方　法

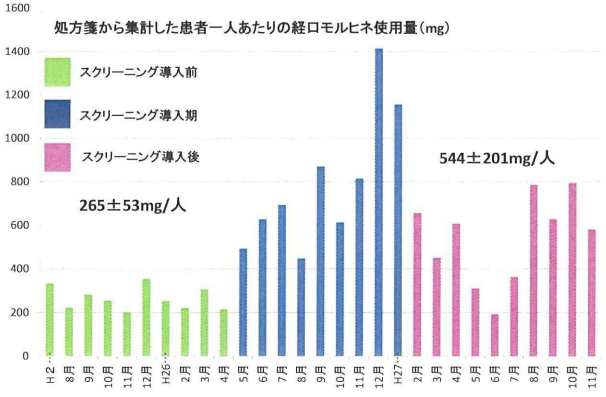
【期間】H25年7月からH27年11月

【対象患者】当院における全がん患者
【調査内容】各月の全がん患者の平均除痛率と処方箋から集計した患者1人当たりのオピオイド処方量（経口モルヒネ換算量）との関係。

結　果



除痛率において
導入半年後からはほとんどの月で
50%を超えており、わずかながら
上昇傾向を示した。



スクリーニング導入前10ヶ月(322人)
平均経口モルヒネ換算量
265±53mg/人
スクリーニング導入後10ヶ月(286人)
平均経口モルヒネ換算量
544±201mg/人

スクリーニング開始後モルヒネ処方量
は増加する傾向があった。

考　察

- 入院がん患者の疼痛スクリーニングがオピオイド処方量を増やし、疼痛緩和に貢献する可能性が示された。
- 本研究の課題として次の二点が挙げられる。
  ①患者数が少なく入院日数にばらつきがあること
  ②看護師による疼痛評価が一定ではないこと
- 疼痛スクリーニングの効果を明確にするためには、更なる研究が必要であると考えられる。

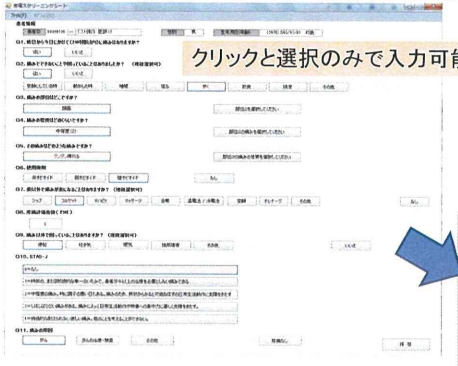
第21回日本緩和医療学会学術大会
COI 開示

演題名：入院患者の疼痛スクリーニングが
オピオイド処方量に及ぼす影響
発表者名：川平茜、福地愛、伊波友理華、笹良剛史、余語久則、
朝川恵利、玉寄菜穂、上運天小百合、橋本孝夫

演題発表内容に関連し、主発表者及び発表責任者には、開示すべきCOI 関係にある企業等はありません。

疼痛スクリーニングシートと集計表

入院がん患者全員について病棟看護師が入力



クリックと選択のみで入力可能

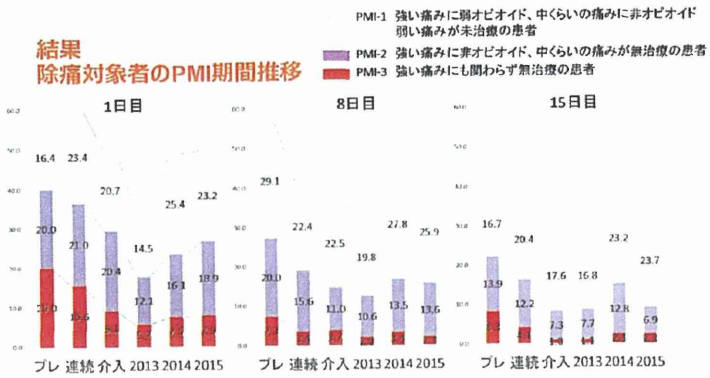
除痛率：「痛みでできないことや困っていることがある」患者と「鎮痛薬を使用している」患者を分母として、その中で「鎮痛薬を使用していてできないことや困っていることはない」患者を分子として計算した割合

PMI: 1 強い痛み(NRS 7-10)に弱オピオイド、中等度の痛み(NRS 4-6)に非オピオイド、弱い痛み(NRS 1-3)が未治療
PMI: 2 強い痛みに非オピオイド、中等度の痛みが未治療
PMI: 3 強い痛みが未治療

結果が自動的に集計され一覧となって閲覧できる

※青森県立中央病院の Special Project for Awareness and Relief of Cancer Symptoms (SPARCS) に準拠

青森県立中央病院の Special Project for Awareness and Relief of Cancer Symptoms［SPARCS］



Ⅳ．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
武田 文和 的場 元弘			やさしいがんの痛みの自己管理 改訂4版	医薬ジャーナル社	大阪府	2015	

雑誌（英文）

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Mikan F, Wada M, Yamada M, Takahashi A, Onishi H, Ishida M, Sato K, Shimizu S, Matoba M, Miyashita M	The Association Between Pain and Quality of Life for Patients With Cancer in an Outpatient Clinic, an Inpatient Oncology Ward, and Inpatient Palliative Care Units.	Am J Hosp Palliat Care			2016 Epub ahead of print
Kamiyama H, Kurosawa K, Ozawa T, Kobayashi K, Gonda K, Teshigawara M, Sato A, Maekawa K, Matoba M	Difference in the timing of cessation of palliative chemotherapy between patients with incurable cancer receiving therapy only in a local hospital and those transitioned from a tertiary medical center to a local hospital.	J Community Support Oncol	13巻11号	405-10	2015
Murakami S, Sudo Y, Miyano K, Nishimura H, Matoba M, Shiraishi S, Konno H, Uezono Y	Tris-hydroxymethyl-aminomethane enhances capsaicin-induced intracellular Ca(2+) influx through transient receptor potential V1 (TRPV1) channels.	J Pharmacol Sci	130巻2号	72-7	2016
Inoue I, Higashi T, Iwamoto M, Heiney SP, Tamaki T, Osawa K, Inoue M, Shiraishi K, Kojima R, Matoba M	A national profile of the impact of parental cancer on their children in Japan.	Cancer Epidemiol	39巻6号	838-41	2015

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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The Association Between Pain and Quality of Life for Patients With Cancer in an Outpatient Clinic, an Inpatient Oncology Ward, and Inpatient Palliative Care Units

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Abstract

Purpose: This study was designed to clarify the association between pain and quality of life (QOL) of Japanese patients with cancer using a cancer-specific QOL scale (European Organization for Research and Treatment of Cancer [EORTC] QLQ-C15-PAL) in 3 care settings (outpatient, inpatient, and palliative care units [PCUs]). **Methods:** We examined the above-mentioned purpose for the total of 404 patients. **Results:** In outpatients, physical, emotional functioning (EF), and global health status/QOL (QL item) were significantly correlated with average pain, and their correlation coefficients were −0.37 to −0.46 ($P < .0001$). In inpatients, they were −0.33 ($P = .006$), −0.26 ($P = .030$), and −0.31 ($P = .012$). In the PCU patients, they were −0.12 ($P = .316$), −0.30 ($P = .009$), and −0.28 ($P = .015$). **Conclusion:** Patients' pain had an association with physical and emotional QOL, and the association was smaller in the PCU patients than the others.

Keywords

quality of life, palliative care, quality of health care, pain intensity, pain score, patients with cancer

Introduction

Palliative care is an approach for improving the quality of life (QOL) of patients and their families facing problems associated with life-threatening illnesses.[1] It has been reported that 33% of patients after curative treatment, 59% of patients under anticancer treatment, and 64% of patients characterized as advanced/metastatic/terminal disease have pain.[2] When patients are in pain, they are not able to enjoy everyday life, think about their future, or have control over their activities. Also, previous studies have revealed that pain in patients with cancer is a burden on patients' QOL and the relationship with their family.[3,4]

The relationship between pain and QOL in patients with cancer has been investigated from various perspectives, such as the experience of patients with metastatic cancer, particular type of cancer (eg, breast cancer, pancreatic cancer, multiple myeloma, and cervical cancer), hospice care setting, comparison of QOL between those with controlled and uncontrolled pain, and several pain relief interventions.[5-17] However, all of these studies had limitations. The primary limitation was that data were collected from only one type of setting (eg, cancer center, university hospital, hospice care center, etc). In addition, several studies did not use a specific QOL scale for patients with cancer. Therefore, these studies may not have evaluated the QOL of patients with cancer appropriately.

The aims of this study were (1) to clarify the association between pain and QOL of Japanese patients with cancer using a cancer-specific QOL scale and (2) to clarify the association between pain and QOL of Japanese patients with cancer in 3 care settings, that is, an outpatient oncology service, inpatient oncology ward, and inpatient palliative care units (PCUs).

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Methods

Participants

We recruited patients with cancer in the following 3 settings: (1) oncology outpatient clinic, (2) oncology inpatient ward in Saitama Medical University, International Medical Center, and (3) 7 inpatient PCU in Japan.

Saitama Medical University, International Medical Center, is one of the designated cancer centers in Japan, with a palliative care team. In addition, it has been designated as a training educational facility. The overview of the hospital is as follows—the total number of beds: 700 beds and cancer inpatient number: 3161 people/year (2013).[18]

And also, admission criteria of PCUs in Japan are different for each facility. However, the conditions for receiving hospice palliative care are shown in the following by Hospice Palliative Care Japan.[19]

1. In patients suffering such as malignant tumors and AIDS, it is directed to patients in need of hospice palliative care.
2. The patient and the family or either of them want to receive hospice palliative care.
3. At the time of providing information of hospice palliative care, it is desirable that the patient has an understanding of the disease name and the medical condition. If the patient does not understand them, the physician properly needs to explain about them in accordance with the patient's need.
4. Patients will not be differentiated by the social, economic, and religious reasons.

The cross-sectional anonymous questionnaire was administered to recruited patients. The inclusion criteria were (1) patient with cancer who was being treated in an inpatient ward or outpatient clinic and (2) patient aged 20 years or older. The exclusion criteria were as follows: (1) patient was not informed of the diagnosis of malignancy, (2) patient would have had serious psychological distress as determined by the primary physician, (3) patient was incapable of filling out a self-reported questionnaire due to cognitive dysfunction or inability to read Japanese, and (4) refusal to participate. Using medical records, we identified patients with cancer who met the criteria and consecutively recruited patients to participate in this study.

Procedure

This survey was performed from August 2007 to March 2008. The survey procedures were as follows: Trained research assistants explained the aims and methods of this survey to potential participants and distributed questionnaires to participants for completion by hand after they agreed to participate. The ethical and scientific validity of this study was approved by the Institutional Review Boards of the University of Tokyo and all participating institutions. This study was conducted in accordance with ethical guidelines for epidemiological research issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare of Japan.

Measurements

Participant characteristics. We asked patients about gender, age, marital status, working status, treatment status, and self-reported Eastern Cooperative Oncology Group (ECOG) performance status. We also collected data about medical history and treatment details using the medical record.

Quality of life. We used a Japanese version of the European Organization for Research and Treatment of Cancer QLQ-C15-PAL (EORTC QLQ-C15-PAL[20]). This is a validated, 15-item questionnaire measuring QOL of patients with cancer in palliative care. These items were directly extracted from the EORTC QLQ-C30,[21,22] a 30-item questionnaire measuring QOL of patients with cancer, to develop a shortened version of the questionnaire suitable for patients in palliative care. The EORTC QLQ-C15-PAL has both multi-item scales and single-item measures. It includes 2 functional scales, that is, physical functioning (PF2; walking condition, living condition, and independence of activity of daily living) and emotional functioning (EF; tense and depressed); 2 symptom scales, that is, fatigue (FA; weak and tired) and pain (PA; presence of pain and interference with daily activity by pain); a global health status/QOL scale (QL item scale; general life condition until 1 week before); and 5 single items, that is nausea and vomiting (NV), dyspnea (DY), insomnia (SL), loss of appetite (AP), and constipation (CO). There are 7 responses to the QL item scale ranging from "excellent" to "very poor." There are 4 responses to the other questions ranging from "very much" to "not at all."

Pain in patients with cancer (after this, it is abbreviated as "pain"). In this study, we defined pain as all of "pain caused by cancer itself, cancer treatment, and without cancer." This is because it is difficult for the patient to identify the cause of the pain in the questionnaire survey.

Brief Pain Inventory (BPI) is a brief pain assessment tool to evaluate cancer pain, which was developed by Cleeland and Ryan.[23] Brief Pain Inventory J (BPI-J) is a Japanese version of the BPI, which was developed by Uki and others.[24] From the BPI-J items, we chose 4 items: "worst pain," "least pain," "average pain," and "interference with general activity" within the previous 24 hours. Each item used a numerical rating scale with 11 options from 0: "no pain (does not interfere)" to 10: "pain as bad as you can imagine (completely interferes)."

Analysis

For analysis, we divided the 11 response options of the BPI-J into 4 groups according to the degree of the pain (0, no pain or does not interfere; 1-3, mild pain or mild interference; 4-6, moderate pain or moderate interference; and 7-10, severe pain or severe interference). We did this in order to compare the difference by the degree of pain or interference with general activity. In addition, the conversion (0-100) of the score of each end point of EORTC QLQ-C15-PAL was based on the scoring rule of this scale. A high score for a functional scale represents a high/healthy level of functioning, a high score for QL item represents a high QOL, but a high score for symptom scales represents a high level of symptomatology.

Table 1. Characteristics of Participants.

	Total (N = 404)	Outpatients (N = 257)	Inpatients (N = 71)	Palliative Care Unit Patients (N = 76)	F	P
Age (mean ± SD), years	61.3 ± 11.8	60.1 ± 11.1	58.5 ± 11.8	67.8 ± 12.2		
Gender: male	49% (n = 194)	45% (n = 114)	61% (n = 43)	49% (n = 37)		
Inmate: have	91% (n = 361)	89% (n = 223)	94% (n = 66)	82% (n = 62)		
Marital status						
Never married	5% (n = 20)	4% (n = 9)	6% (n = 4)	9% (n = 7)		
Married	79% (n = 312)	83% (n = 208)	83% (n = 57)	63% (n = 47)		
Divorced	6% (n = 24)	6% (n = 14)	7% (n = 5)	16% (n = 5)		
Widowed	10% (n = 38)	8% (n = 19)	4% (n = 3)	21% (n = 16)		
Work status						
Employed	26% (n = 100)	29% (n = 72)	30% (n = 21)	9% (n = 7)		
Retired	15% (n = 59)	13% (n = 33)	24% (n = 17)	12% (n = 9)		
Not employed	59% (n = 233)	57% (n = 141)	46% (n = 32)	79% (n = 60)		
Primary site						
Stomach or esophagus	19% (n = 72)	16% (n = 40)	38% (n = 26)	11% (n = 6)		
Liver, gallbladder, or pancreas	8% (n = 28)	6% (n = 16)	4% (n = 3)	17% (n = 9)		
Lung	6% (n = 21)	2% (n = 6)	3% (n = 2)	24% (n = 13)		
Breast	25% (n = 91)	32% (n = 79)	9% (n = 6)	11% (n = 6)		
Urinary tract	2% (n = 6)	0.4% (n = 1)	3% (n = 2)	6% (n = 3)		
Colon or rectum	26% (n = 95)	32% (n = 79)	14% (n = 10)	11% (n = 6)		
Others	16% (n = 58)	11% (n = 27)	29% (n = 20)	20% (n = 11)		
Months since diagnosis (mean ± SD)	32.9 ± 34.6	35.0 ± 34.8	21.4 ± 32.0	36.0 ± 35.8		
Recurrence or metastasis						
Have	84% (n = 311)	78% (n = 208)	78% (n = 54)	92% (n = 49)		
Nothing	16% (n = 59)	22% (n = 40)	22% (n = 15)	8% (n = 4)		
Current treatment						
Surgery	71% (n = 232)	84% (n = 176)	69% (n = 52)	9% (n = 4)		
Radiation	4% (n = 12)	1% (n = 3)	7% (n = 5)	9% (n = 4)		
Opioid	26% (n = 85)	15% (n = 31)	24% (n = 18)	82% (n = 36)		
Past treatment						
Surgery	32% (n = 266)	36% (n = 181)	39% (n = 40)	30% (n = 45)		
Chemotherapy	42% (n = 296)	41% (n = 203)	39% (n = 40)	36% (n = 53)		
Radiation	20% (n = 150)	17% (n = 87)	22% (n = 22)	28% (n = 41)		
Others	5% (n = 38)	6% (n = 28)	0% (n = 0)	7% (n = 10)		
Performance status (Eastern Cooperative Oncology Group)[a]						
Mean ± SD	1.18 ± 1.07	0.84 ± 0.77	1.18 ± 1.08	2.33 ± 1.12		
0	26% (n = 101)	33% (n = 80)	26% (n = 18)	4% (n = 3)		
1	47% (n = 183)	56% (n = 136)	49% (n = 33)	19% (n = 14)		
2	13% (n = 51)	7% (n = 18)	10% (n = 7)	36% (n = 26)		
3	8% (n = 32)	4% (n = 9)	10% (n = 7)	22% (n = 16)		
4	5% (n = 19)	0.8% (n = 2)	4% (n = 3)	19% (n = 14)		
Physical functioning (PF2)	71.1 ± 28.60	80.05 ± 1.58	66.65 ± 3.00	45 ± 2.90	57.79	<.0001
Emotional functioning (EF)	72.44 ± 21.32	74.97 ± 1.33	66.92 ± 2.54	69.04 ± 2.45	5.13	.006
Fatigue (FA)	42.6 ± 25.73	36.09 ± 1.50	46.34 ± 2.97	61.79 ± 2.78	33.97	<.0001
Nausea and vomiting (NV)	10.97 ± 19.56	8.51 ± 1.21	12.57 ± 2.32	17.79 ± 2.23	7.00	.001
Pain (PA)	26.82 ± 26.84	20.73 ± 1.61	29.47 ± 3.04	44.59 ± 2.94	25.81	<.0001
Dyspnea (DY)	18.43 ± 23.20	14.62 ± 1.42	20.48 ± 2.70	29.33 ± 2.60	12.66	<.0001
Insomnia (SL)	26.23 ± 25.50	22.4 ± 1.57	29.05 ± 2.98	36.4 ± 2.86	9.74	<.0001
Appetite loss (AP)	27.05 ± 30.15	19.24 ± 1.78	38.16 ± 3.41	42.98 ± 3.25	26.90	<.0001
Constipation (CO)	29.56 ± 29.55	24.02 ± 1.79	34.80 ± 3.46	43.42 ± 3.28	14.88	<.0001
Global health status/quality of life ("QL item")	62.09 ± 25.96	67.48 ± 1.59	54.41 ± 3.03	51.33 ± 2.89	15.86	<.0001

Abbreviation: SD, standard deviation.
[a]Score = 0 indicates that participant had no symptoms, and score = 4 indicates that participant required assistance with all activities of daily living.

Table 2. Pain Level According to the BPI.

Score[a]	Mean ± SD	0 % (n)	1-3 % (n)	4-6 % (n)	7-10 % (n)
Total (N = 404)					
Average pain	1.73 ± 1.94	36% (n = 139)	45% (n = 174)	17% (n = 65)	2% (n = 9)
Worst pain	2.21 ± 2.54	36% (n = 142)	39% (n = 151)	15% (n = 59)	10% (n = 39)
Least pain	1.12 ± 1.58	47% (n = 179)	45% (n = 173)	6% (n = 23)	2% (n = 9)
Interference with general activity	1.82 ± 2.60	49% (n = 187)	32% (n = 122)	11% (n = 43)	9% (n = 33)
Outpatients (n = 257)					
Average pain	1.39 ± 1.78	43% (n = 104)	45% (n = 109)	11% (n = 26)	2% (n = 4)
Worst pain	1.71 ± 2.17	43% (n = 105)	41% (n = 100)	12% (n = 29)	5% (n = 12)
Least pain	0.90 ± 1.46	54% (n = 130)	39% (n = 95)	5% (n = 13)	2% (n = 4)
Interference with general activity	1.36 ± 2.25	58% (n = 140)	27% (n = 66)	10% (n = 24)	5% (n = 13)
Inpatients (n = 71)					
Average pain	2.01 ± 1.97	30% (n = 21)	45% (n = 31)	22% (n = 15)	3% (n = 2)
Worst pain	2.49 ± 2.69	33% (n = 23)	39% (n = 27)	16% (n = 11)	13% (n = 9)
Least pain	1.03 ± 1.52	36% (n = 24)	57% (n = 38)	6% (n = 4)	1% (n = 1)
Interference with general activity	2.04 ± 2.55	38% (n = 26)	43% (n = 29)	9% (n = 6)	10% (n = 7)
Palliative care units patients (n = 76)					
Average pain	2.60 ± 2.11	19% (n = 14)	45% (n = 34)	32% (n = 24)	4% (n = 3)
Worst pain	3.63 ± 2.97	19% (n = 14)	32% (n = 24)	25% (n = 19)	24% (n = 18)
Least pain	1.64 ± 1.85	33% (n = 25)	53% (n = 40)	8% (n = 6)	5% (n = 4)
Interference with general activity	3.11 ± 3.21	28% (n = 21)	36% (n = 27)	18% (n = 13)	18% (n = 13)

Abbreviations: BPI, Brief Pain Inventory; SD, standard deviation.
[a]BPI score ranges from 0 (no pain) to 10 (worst imaginable pain). Average pain is the average level of pain that the participant experiences. Worst pain is the level of pain that was the greatest in the previous 24 hours. Least pain is the level that was the lowest in the previous 24 hours.

First, we described the distribution of BPI-J in total and in 3 clinical settings (outpatient, inpatient oncology ward, and PCU). Second, we explored the correlation between BPI-J and EORTC QLQ-C15-PAL by calculating Spearman correlation coefficient. Third, multiple regression analyses were performed with each end point of EORTC QLQ-C15-PAL as dependent variable and average pain, age, gender, inmate, marital status, work status, primary site, months since diagnosis, and recurrence or metastasis as independent variables, with forced entry approaches to control for confounding factors. Dummy variables were created for each of gender, inmate, marital status, work status, primary site, and recurrence or metastasis. The analysis software was JMP Pro 9.02. We set significance level as .05 and conducted 2-sided test in all analyses.

Results

Respondent Characteristics

A total of 404 patients with cancer participated in this study. Participant characteristics are shown in Table 1. The mean age ± standard deviation (SD) was 61 ± 12 years, and 49% of the total participants were men. Primary tumor sites were colon/rectum (26%), breast (25%), and stomach/esophagus (19%). The mean duration of disease ± SD was 33 ± 35 months. Eighty-four percent of the patients had recurrence and metastases, and 42% were undergoing chemotherapy. Thirteen percent had ECOG performance status of 3 or 4, although 73% had 0 or 1.

Pain Intensity

Table 2 shows pain condition by BPI. As for average pain, 36% had a score of 0 (no pain), 45% had 1 to 3 (mild pain), 17% had 4 to 6 (moderate pain), and 2% had 7 to 10 (severe pain). The percentage of outpatients who had pain worse than average pain score 4 was 13%, whereas that of inpatients was 25% and that of PCU patients was 37%.

For worst pain, 36% had a score of 0 (no pain), 39% had 1 to 3 (mild pain), 15% had 4 to 6 (moderate pain), and 10% had 7 to 10 (severe pain). The percentage of outpatients who had pain worse than worst pain score 4 was 17%, whereas that of inpatients was 29% and that of PCU patients was 49%.

For interference with general activity, 49% had a score of 0 (no pain), 32% had 1 to 3 (mild pain), 11% had 4 to 6 (moderate pain), and 9% had 7 to 10 (severe pain). The percentage of outpatients who had an interference with general activity score greater than 4 was 15%, whereas that of inpatients was 19% and that of PCU patients was 36%.

Association Between Pain and QOL

Table 3 shows the correlation between QOL and the BPI pain score. For the total sample, average pain was significantly correlated with PF2 ($\rho = -0.39$, $P < .0001$), EF ($\rho = -0.35$, $P < .0001$), FA ($\rho = 0.45$, $P < .0001$), SL ($\rho = 0.45$, $P < .0001$), and QL item ($\rho = -0.44$, $P < .0001$). Association between average pain or worst pain and major aspects of the QOL was similar, and the association with least pain was relatively small.

Table 3. The Correlation Between Pain (BPI) and QOL (EORTC QLQ-C15 PAL).[a]

	Average Pain		Worst Pain		Least Pain		Interference With General Activity	
	ρ	P	ρ	P	ρ	P	ρ	P
Total (N = 404)								
PF2	−0.39	**<.0001**	−0.41	**<.0001**	−0.31	**<.0001**	−0.38	**<.0001**
EF	−0.35	**<.0001**	−0.37	**<.0001**	−0.28	**<.0001**	−0.37	**<.0001**
FA	0.45	**<.0001**	0.46	**<.0001**	0.33	**<.0001**	0.48	**<.0001**
NV	0.27	**<.0001**	0.26	**<.0001**	0.19	**<.0001**	0.26	**<.0001**
PA	0.74	**<.0001**	0.74	**<.0001**	0.54	**<.0001**	0.68	**<.0001**
DY	0.24	**<.0001**	0.24	**<.0001**	0.22	**<.0001**	0.22	**<.0001**
SL	0.45	**<.0001**	0.44	**<.0001**	0.39	**<.0001**	0.40	**<.0001**
AP	0.34	**<.0001**	0.33	**<.0001**	0.23	**<.0001**	0.37	**<.0001**
CO	0.28	**<.0001**	0.28	**<.0001**	0.21	**<.0001**	0.32	**<.0001**
QL item	−0.44	**<.0001**	−0.42	**<.0001**	−0.30	**<.0001**	−0.48	**<.0001**
Outpatients (n = 257)								
PF2	−0.37	**<.0001**	−0.37	**<.0001**	−0.28	**<.0001**	−0.36	**<.0001**
EF	−0.38	**<.0001**	−0.37	**<.0001**	−0.30	**<.0001**	−0.36	**<.0001**
FA	0.39	**<.0001**	0.38	**<.0001**	0.26	**<.0001**	0.43	**<.0001**
NV	0.25	**<.0001**	0.21	**.001**	0.19	**.004**	0.26	**<.0001**
PA	0.71	**<.0001**	0.72	**<.0001**	0.53	**<.0001**	0.66	**<.0001**
DY	0.18	**.005**	0.16	**.015**	0.17	**.010**	0.10	.107
SL	0.50	**<.0001**	0.48	**<.0001**	0.43	**<.0001**	0.41	**<.0001**
AP	0.34	**<.0001**	0.32	**<.0001**	0.22	**.001**	0.41	**<.0001**
CO	0.20	**.001**	0.17	**.009**	0.13	**.044**	0.27	**<.0001**
QL item	−0.46	**<.0001**	−0.43	**<.0001**	−0.30	**<.0001**	−0.47	**<.0001**
Inpatients (n = 71)								
PF2	−0.33	**.006**	−0.30	**.012**	−0.24	**.052**	−0.28	**.020**
EF	−0.26	**.030**	−0.31	**.009**	−0.18	.138	−0.35	**.004**
FA	0.44	**<.0001**	0.44	**<.0001**	0.44	**<.0001**	0.50	**<.0001**
NV	0.31	**.009**	0.28	**.021**	0.31	**.011**	0.28	**.020**
PA	0.73	**<.0001**	0.71	**<.0001**	0.61	**<.0001**	0.67	**<.0001**
DY	0.39	**.001**	0.43	**<.0001**	0.29	**.018**	0.39	**.001**
SL	0.30	**.012**	0.34	**.004**	0.30	**.013**	0.27	**.024**
AP	0.30	**.013**	0.29	**.014**	0.26	**.034**	0.34	**.005**
CO	0.27	**.026**	0.31	**.011**	0.18	.154	0.28	**.020**
QL item	−0.31	**.012**	−0.35	**.004**	−0.22	.077	−0.31	**.011**
PCU patients (n = 76)								
PF2	−0.12	.316	−0.17	.151	−0.20	.087	−0.17	.141
EF	−0.30	**.009**	−0.35	**.003**	−0.20	.096	−0.38	**.001**
FA	0.38	**.001**	0.37	**.001**	0.19	.107	0.33	**.005**
NV	0.16	.165	0.29	**.011**	−0.03	.831	0.18	.138
PA	0.72	**<.0001**	0.67	**<.0001**	0.37	**.001**	0.66	**<.0001**
DY	0.01	.927	0.06	.627	0.06	.642	0.13	.279
SL	0.28	**.017**	0.26	**.022**	0.18	.121	0.39	**.001**
AP	0.10	.393	0.12	.323	−0.01	.956	0.07	.553
CO	0.23	**.046**	0.31	**.007**	0.21	.077	0.27	**.021**
QL item	−0.28	**.015**	−0.22	.056	−0.05	.667	−0.44	**<.0001**

Abbreviations: AP, appetite loss; CO, constipation; DY, dyspnea; EF, emotional functioning; FA, fatigue; NV, nausea and vomiting; PA, pain; PCU, palliative care unit; PF2, physical functioning; QL item, global health status/quality of life; SL, insomnia.
[a]Bold values indicate $P < .05$.

In outpatients, average pain was significantly correlated with PF2 ($\rho = -.37$, $P < .0001$), EF ($\rho = -.38$, $P < .0001$), FA ($\rho = 0.39$, $P < .0001$), SL ($\rho = .50$, $P < .0001$), and QL item ($\rho = -.46$, $P < .0001$). The association between average pain or worst pain and major aspects of the QOL was similar, and the association with least pain was relatively small.

In inpatients, average pain was significantly correlated with FA ($\rho = .44$, $P = .0003$) and DY ($\rho = .39$, $P = .001$). Worst pain was significantly correlated with FA ($\rho = .44$, $P = .0003$), DY ($\rho = .43$, $P = .0002$), and QL item ($\rho = -.35$, $P = .004$). Least pain was significantly correlated with FA only ($\rho = .44$, $P = .0004$), and the association with least pain was relatively small.

In the PCU patients, average pain was significantly correlated with FA only ($\rho = .38$, $P = .001$). Worst pain was significantly correlated with EF ($\rho = -.35$, $P = .003$) and

Table 4. Association Between Pain and Quality of Life Adjusted for Patient Backgrounds.

	QL item			PF2			EF		
Variable (reference category, ref)	β	Standard Error	P	β	Standard Error	P	β	Standard Error	P ref =
Average pain	−.37	0.72	<0.0001	−.26	0.68	<0.0001	−0.36	0.61	<0.0001
Inpatient (ref = outpatient)	−.14	3.75	0.015	−.16	3.54	0.003	−0.09	3.19	0.122
PCU (ref = outpatient)	−.12	4.32	0.044	−.29	4.07	<0.0001	0.03	3.67	0.653
Age	.05	0.13	0.366	−.04	0.12	0.469	0.04	0.11	0.506
Gender (ref = female)	−.01	3.44	0.840	.09	3.25	0.145	0.11	2.93	0.121
Inmate (ref = nothing)	−.02	5.65	0.796	−.06	5.33	0.286	−0.03	4.80	0.682
Marital status (ref = not married)	.02	4.02	0.755	.04	3.79	0.555	0.00	3.41	0.960
Work status (employed/ ref = not employed)	.10	3.44	0.113	.07	3.24	0.204	0.03	2.92	0.687
Work status (retired/ ref = not employed)	.11	4.17	0.050	−.01	3.94	0.875	−0.04	3.54	0.491
Months since diagnosis	.06	0.04	0.311	.08	0.04	0.159	0.15	0.04	0.011
Primary site (liver, gallbladder, or pancreas/ ref = stomach or esophagus)	−.02	5.64	0.686	−.12	5.32	0.036	−0.08	4.79	0.197
Primary site (lung/ ref = stomach or esophagus)	−.07	6.67	0.269	−.13	6.29	0.020	−0.09	5.66	0.142
Primary site (breast/ ref = stomach or esophagus)	.02	4.83	0.791	−.12	4.56	0.137	−0.14	4.10	0.096
Primary site (urinary tract/ ref = stomach or esophagus)	−.03	9.85	0.620	−.17	9.29	0.001	−0.14	8.37	0.010
Primary site (colon or rectum/ ref = stomach or esophagus)	.03	4.13	0.659	.02	3.90	0.751	−0.11	3.51	0.148
Primary site (others/ ref = stomach or esophagus)	−.07	4.84	0.274	−.05	4.57	0.458	−0.17	4.11	0.014
Recurrence or metastasis (ref = nothing)	−.07	3.74	0.223	−.11	3.52	0.032	−0.09	3.17	0.118
R^2		.26			.34			0.22	
Adjusted R^2		.21			.30			0.17	

	FA			NV			DY		
Variable (reference category, ref)	β	Standard Error	P	β	Standard Error	P	β	Standard Error	P
Average pain	.35	0.66	<.0001	.27	0.50	< 0.0001	0.28	0.68	< 0.0001
Inpatient (ref = outpatient)	.06	3.47	.245	.02	2.60	0.719	0.06	3.57	0.281
PCU (ref = outpatient)	.18	3.99	.001	.01	2.99	0.884	0.08	4.11	0.177
Age	−.06	0.12	.284	−.02	0.09	0.817	0.01	0.12	0.877
Gender (ref = female)	−.05	3.19	.472	−.06	2.39	0.406	0.09	3.28	0.202
Inmate (ref = nothing)	.03	5.22	.643	.04	3.91	0.569	−0.02	5.38	0.773
Marital status (ref = not married)	−.06	3.72	.326	.05	2.78	0.447	−0.10	3.83	0.128
Work status (employed/ ref = not employed)	−.08	3.18	.149	.03	2.38	0.658	−0.10	3.28	0.105
Work status (retired/ ref = not employed)	.04	3.86	.436	.03	2.89	0.647	−0.07	3.98	0.262
Months since diagnosis	−.04	0.04	.468	−.06	0.03	0.318	−0.09	0.04	0.135
Primary site (liver, gallbladder, or pancreas/ ref = stomach or esophagus)	.05	5.22	.393	−.08	3.91	0.189	−0.01	5.38	0.899
Primary site (lung/ ref = stomach or esophagus)	−.02	6.17	.734	−.10	4.62	0.113	0.22	6.35	0.001
Primary site (breast/ ref = stomach or esophagus)	−.05	4.47	.604	−.22	3.35	0.018	0.14	4.60	0.118
Primary site (urinary tract/ ref = stomach or esophagus)	.19	9.11	.000	.03	6.82	0.644	0.00	9.38	0.954
Primary site (colon or rectum/ ref = stomach or esophagus)	−.15	3.82	.026	−.08	2.86	0.276	−0.01	3.94	0.934
Primary site (others/ ref = stomach or esophagus)	−.01	4.48	.867	−.12	3.35	0.098	0.05	4.61	0.463
Recurrence or metastasis (ref = nothing)	.15	3.46	.004	.14	2.59	0.020	0.04	3.56	0.489
R^2		.33			.14			0.21	
Adjusted R^2		.30			.09			0.17	

	SL			AP			CO		
Variable (reference category, ref)	β	Standard Error	P	β	Standard Error	P	β	Standard Error	P
Average pain	.40	0.69	<.0001	.32	0.79	<0.0001	0.27	0.84	<0.0001
Inpatient (ref = outpatient)	.08	3.61	.189	.16	4.12	0.005	0.07	4.40	0.239
PCU (ref = outpatient)	.14	4.16	.020	.19	4.75	0.002	0.02	5.07	0.708
Age	−.02	0.12	.709	.01	0.14	0.875	0.00	0.15	0.954
Gender (ref = female)	−.13	3.32	.062	−.01	3.79	0.928	0.06	4.04	0.434

(continued)

Table 4. (continued)

	SL			AP			CO		
Variable (reference category, ref)	β	Standard Error	P	β	Standard Error	P	β	Standard Error	P
Inmate (ref = nothing)	.05	5.43	.422	.14	6.21	0.027	0.09	6.63	0.172
Marital status (ref = not married)	.03	3.87	.674	−.03	4.42	0.604	−0.01	4.72	0.867
Work status (employed/ ref = not employed)	.00	3.31	.988	.01	3.78	0.932	−0.12	4.03	0.062
Work status (retired/ ref = not employed)	.05	4.02	.408	.06	4.59	0.259	0.00	4.90	0.962
Months since diagnosis	−.10	0.04	.101	−.15	0.05	0.008	−0.10	0.05	0.111
Primary site (liver, gallbladder, or pancreas/ ref = stomach or esophagus)	.12	5.43	.053	.06	6.20	0.316	−0.01	6.62	0.935
Primary site (lung/ ref = stomach or esophagus)	.03	6.42	.622	.01	7.33	0.925	0.12	7.82	0.069
Primary site (breast/ ref = stomach or esophagus)	−.02	4.65	.794	−.06	5.31	0.431	0.06	5.67	0.507
Primary site (urinary tract/ ref = stomach or esophagus)	−.08	9.48	.160	.02	10.83	0.654	0.17	11.56	0.004
Primary site (colon or rectum/ ref = stomach or esophagus)	.03	3.98	.651	−.08	4.54	0.259	−0.04	4.85	0.586
Primary site (others/ ref = stomach or esophagus)	.05	4.66	.462	.12	5.32	0.073	0.08	5.68	0.274
Recurrence or metastasis (ref = nothing)	.06	3.60	.259	.09	4.11	0.082	−0.04	4.38	0.482
R^2		.25			.31			0.19	
Adjusted R^2		.20			.27			0.14	

Abbreviations: AP, appetite loss; CO, constipation; DY, dyspnea; EF, emotional functioning; FA, fatigue; NV, nausea and vomiting; PCU, palliative care unit; PF2, physical functioning; QL item, global health status/quality of life; SL, insomnia.

FA ($\rho = .37$, $P = .001$). The association with least pain was relatively small.

In addition, we performed multiple regression analyses with forced entry approaches to control for confounding factors of patient characteristics. There were significant relationships ($P < .0001$) between each end point of EORTC QLQ-C15-PAL and average pain (Table 4).

Discussion

We examined the association between pain and QOL of patients with cancer in an outpatient service, an inpatient oncology ward, and inpatient PCU. Patients completed the Japanese edition of the EORTC QLQ-C15-PAL questionnaire and BPI. To our knowledge, this is the first study that has investigated the association between pain and QOL in patients with cancer in these 3 settings. Our results showed that pain had an association with QOL. It had a moderate influence not only on physical aspects such as PF2 and FA, SL, and DY but also on EF. Results also showed that the association with pain was smaller for the PCU patients compared to the outpatients and inpatients.

First of all, the association between pain and QOL has also been reported by previous studies[5,12,14] using different scales. The main finding of this study is that the relationship between the end points of BPI, except least pain, and the QOL scale showed a similar tendency in outpatients and inpatients. Several studies have shown that severe pain has an association with QOL.[6,11,25] The end points of BPI, except least pain, showed clear relationships with PF2, EF, FA, SL, and QL item in outpatients. In inpatients, clear relationships with FA and DY were shown. In addition, least pain showed a clear relationship with SL in outpatients and FA in inpatients. The relationships between BPI end points, except least pain, and QOL in outpatients and inpatients had a similar tendency. Also, end points of the QOL scale that showed clear relationships with least pain were few. These outcomes showed that the association between severe pain and QOL had a wide influence than that between least pain and QOL and also that between least pain and QOL is limited to SL in outpatients and FA in inpatients. However, the relationships with SL in outpatients and FA in inpatients were clear. Therefore, we can say that not only control so as to reduce the level of average pain and worst pain for the outpatient and inpatient, should also consider the effect of least pain. To promote the patient's understanding of the association between least pain and SL or FA and not to downplay the influence of least pain will lead to further improvement in QOL.

Moreover, we analyzed the association between pain and QOL of patients with cancer in 3 settings. The results of PCU patients were different from outpatients and inpatients. Table 3 showed the correlation (Spearman) between pain and QOL. Significant correlation coefficients have very fewer tendency in the PCU patients as compared to the outpatients and inpatients. We understand that the PCU patients have much variety distress due to high disease severity, and this may have an influence on this result. Although the results of the regression analysis of hospice patients by McMillan and Small indicated that total distress score, pain intensity, dyspnea intensity, and constipation intensity were related to QOL at the univariate level, the strongest predictor was the total distress score.[10] The outcome of total distress score shows that hospice patients also have various distress. Our result indicates that the pain PCU patient is also suffering is complex, therefore, it is particularly essential for the PCU patient to be approached by multiprofessional team.

And also, we performed multiple regression analyses with forced entry approaches to control for confounding factors of patient characteristics. There were significant relationships ($P < .0001$) between each end point of QOL and average pain. This indicates that pain is an independent factor associated with the QOL in result controlling for confounding factors of patient characteristics.

Finally, we describe the limitations of this study. It is that inpatients and outpatients came from the same institution, and we excluded patients who have serious psychological distress. These things might have caused a bias in the findings of this study. And also, since it is difficult for the patient to identify the cause of the pain, we asked without distinction the cause of the pain in the BPI. Therefore, we could not analyze for each cause of pain in this study. In addition, since the causal relationship between pain and QOL could not be identified, it is not possible to conclude that there is a causal relationship between pain and QOL in this survey.

Conclusion

We examined the association between pain and QOL for patients with cancer in an outpatient clinic, an inpatient oncology ward, and inpatient PCU. Patients completed the Japanese edition of the EORTC QLQ-C15-PAL questionnaire and BPI. To our knowledge, this is the first study that has investigated the association between pain and QOL in 3 settings. Our results showed that (1) pain had an association with physical and emotional QOL and (2) the association with pain was smaller in the PCU patients than the outpatients and inpatients.

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Difference in the timing of cessation of palliative chemotherapy between patients with incurable cancer receiving therapy only in a local hospital and those transitioned from a tertiary medical center to a local hospital

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Background It is important to know when to decide to end palliative chemotherapy (PC) for the quality of life of patients. However, there is currently no clear agreement on when to terminate PC.
Objectives To determine whether the difference of the period between the completion of PC and death affects patients' trajectory of supportive care near end of life.
Methods This retrospective study included 52 adult patients with incurable cancer who had received PC and who were referred to our palliative care team and died in our local hospital between July 2011 and June 2014. Group A comprised patients who received anticancer therapy such as surgery and PC only in our hospital and eventually died there. Group B comprised patients who were transitioned to our hospital from tertiary medical centers after cessation of PC.
Results 17 of 22 patients (77%) in Group A conveyed the intention of continuing PC in the first interview with a physician of the palliative care team, whereas 4 of 30 patients (13%) in Group B conveyed a similar intention. The patients in Group B stopped PC a median of 43 days earlier than did the patients in Group A ($P < .0001$).
Conclusions These data showed that more patients in Group A wanted to continue PC and had a shorter interval between last PC and death. Change in the hospital where the patients are given supportive care might contribute to the cessation of futile PC at an appropriate time.

As Japan's society ages, increasing numbers of middle-aged and elderly people living in the country will be diagnosed with, and eventually die of cancer.[1,2] With the commensurate growing call for better end-of-life (EoL) care, the role of hospitals in Japanese communities has been redefined.[3,4] It has become necessary to shorten stays in acute-care hospitals for patients who do not need aggressive anticancer therapy. In addition, hospital restructuring has transferred many aspects of inpatient care to community-based care, including EoL and palliative care of those with cancer.[1,3]

Patients who are transitioned from a tertiary medical center (TMC) to a local hospital by their oncologists not only leave the institution, but the physicians and medical staff who had been caring for them and who were familiar with their cases. Moreover, these patients may be informed of the serious condition of their disease at the time of transition. Talking to patients and their families about

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supportive care and death is not easy, particularly when patients and/or their families want to continue aggressive therapy.[5]

Palliative chemotherapy (PC) near EoL is a commonly discussed issue nowadays. It remains the mainstay of treatment for patients with advanced malignancy in developed countries. Toxic side effects that significantly reduce patients' quality of life (QoL) and increase fatigue and anxiety are unacceptable when the aim of treatment is palliation of symptoms. Therefore, appropriately timed cessation of PC is critical.[6,7] In most cases, use of PC in the last few weeks of a patient's life may indicate poor clinical judgment.[8] Because it is even more complex to treat patients with a short life expectancy, treatment goals for any given patient should be clearly defined.[5,9]

Chichibu Municipal Hospital (CMH) is a medium-sized public hospital in rural Japan; cancer patients are cared for and treated as outpatients or inpatients by a few oncologists. A full-time physician specializing in gastrointestinal surgeries and a part-time (once a week) physician specializing in PC were in charge of PC at CMH. The palliative care team of CMH comprises medical doctors and other health care professionals, such as nurses, pharmacists, and therapists. The hospital has 135 beds for acute care. It is the core community hospital in the region, but not a general hospital. Patients needing highly advanced medical care are transferred to a TMC that is about 40 km (about 25 miles) away. Patients diagnosed with gastrointestinal, pancreatic, or urological cancer at CMH can choose between CMH and a TMC for their treatment. Almost all patients who choose CMH receive anticancer therapy only throughout the course of their disease. Some patients who receive anticancer therapy at TMCs return to CMH after cessation of anticancer therapy. At TMCs, patients who do not benefit from further standard treatment or who are ineligible for participation in clinical trials may tend to cease PC earlier, even if their condition is generally good. The aim of this retrospective study was to determine whether the difference of the period between the completion of PC and death affects patients' trajectory of supportive care near EoL. The results may help physicians better understand when they should cease PC and focus instead on providing supportive care to their patients near EoL.

Methods

This study used a retrospective cohort design. All adult patients with incurable cancer, such as metastatic and recurrent cancer, who had received PC and supportive care from the palliative care team at CMH and subsequently died there during July 2011-June 2014 were identified from the medical records. PC was defined as chemotherapy treatment with noncurative intent.

Patients who were diagnosed with incurable cancer and died at CMH but did not receive PC throughout the course of the disease were not included in this study. Patients who had already been referred before the start of the study period and those who were referred during the period and were alive at the end of the study period were not included. In addition, patients who eventually died at home or in a nearby hospital and those referred to our palliative care team who died within 20 days were not included (Figure). For the latter group of patients, confirmation regarding their preference for cessation of PC and location of EoL during the interview with a physician of our palliative care team was considered difficult because of the patients' poor general condition

When the patients were referred to the palliative care team, a physician member of the team would conduct a face-to-face interview of about 20 minutes with each patient during a regularly scheduled treatment appointment at our hospital. After the interview, the physician was in charge of the patient's medical care with other members of the palliative care team, in place of the oncologist. We recorded the following variables: age, gender, site of cancer, date of death, date of first visit to our hospital, date of the first interview with a physician of our palliative care team, number of days spent in our hospital, number of admissions for palliative care, date of cessation of anticancer therapy, and date of patients' perception of supportive care. Patients' perception of palliative care was defined as their decision to switch to best supportive care only. We focused on the following factors: patients' willingness to continue anticancer therapy, the preferred location for EoL therapy, patients' expression of fear of abandonment, the period between cessation of PC and death, the interval between talking to patients about supportive care and death, and the length of hospital stay immediately before death. Expression of fear of abandonment was defined as use of descriptions such as "I was abandoned by my physician (or oncologist)" in the medical records at the time of the first interview with the physician at our palliative care team or in subsequent daily medical records until the death of the patient.

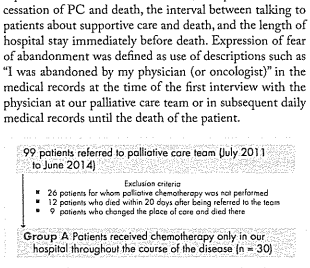

FIGURE Flow chart of patients who were referred to the palliative care team.

Patients were divided into 2 groups: Group A, which comprised patients who received chemotherapy only in our hospital throughout the course of their disease; and Group B, which comprised patients who were transitioned to our hospital after cessation of PC. In Group A, the date of progression of the cancer with the current line of treatment was determined retrospectively. Progressive disease was defined as levels of one or more tumor marker being significantly above normal, according to the RECIST [Response Evaluation Criteria in Solid Tumors] guidelines for imaging.[10] QoL could not be assessed with specific scales because this was a retrospective study. CMH's institutional review board approved the project protocol. Statistical tests included the Fisher exact test, chi-square test, and the Mann–Whitney test, as appropriate. A *P* value of <.05 was considered statistically significant. All statistical analyses were performed with StatView (SAS Institute, Cary, NC).

Results

During July 2011-June 2014, 99 consecutive patients with incurable cancer who were referred to the palliative care team were screened. Of those patients, 26 were excluded because they had not received PC, 12 were excluded because they died within 20 days of being referred to our team because of deterioration in the disease, and 9 were excluded because they changed the hospital of care and died there after an intervention of our team. In all, 52 patients (25 men, 27 women) who met our inclusion criteria were included in this study (Group A, n = 22; Group B, n = 30). The patient characteristics are shown in Table 1. Of the patients in whose charts were reviewed, 64% and 37% (Group A and Group B, respectively) were men, and the respective median ages were 71 years and 72.5 years. The primary cancer sites were pancreatic and biliary (45% and 27%), colorectal (23% and 13%), gynecological (0% and 20%), and lung (0% and 17%y), as shown in Table 2.

TABLE 1 Characteristics and attributes of patients (N = 52)

	Group		
Characteristic/attribute	**A (n = 22)**	**B (n = 30)**	***P* value**
Median age, y (range)	71 (43-82)	72.5 (43-86)	.95[†]
Sex – male, n (%)	14 (63.6)	11 (36.6)	.09[*]
Median distance between home and a TMC, km/miles[a] (range)	Not available	41.5/28.0 (30.6-114/19.0-70.8)	Not applicable
Median distance between home and CMH, km/miles[a] (range)	2.75/1.7 (0.1-18.8/0.06-11.7)	4.75/3.0 (1-17.6/0.62-11.0)	.13[†]
Median time interval between first visit to CMH and death, d (range)	258.5 (55-1,395)	58.5 (21-279)	.0001[†]
Median time interval between referral to PCT to death, d (range)	53 (22-91)	58.5 (21-279)	.18[†]
Median time interval between progressive disease and death, d (range)	58 (15-199)	Not available	Not applicable
Median time interval between last chemotherapy and death, d (range)	54 (6-199)	97 (53-353)	<.0001[†]
Median time interval between perception of supportive care and death, d (range)	32 (0-199)	75.5 (32-340)	<.0001[†]
Median no. of admissions for palliative care (range)	2 (1-4)	2 (1-10)	.43[†]
Total median length of hospital stay for symptom control, d (range)	31 (13-82)	29 (11-74)	.35[†]
Final length of hospital stay before death, d (range)	24 (2-59)	18.5 (2-54)	0.55[†]

TMC, tertiary medical center; CMH, Chichibu Municipal Hospital, PCT, palliative care team

[a]Values for miles are rounded to 1 decimal point.

[*]*P* value by Fisher exact test. [†]*P* value by Mann-Whitney test.

TABLE 2 Primary cancer diagnosis (N = 52)*

Type of malignancy	Group A (n = 22)	Group B (n = 30)
Pancreatic and biliary	10	8
Colorectal	5	4
Gastric	5	1
Esophageal	1	2
Urological	1	0
Gynecologic	0	6
Lung	0	5
Head and neck	0	4

*P value by chi-square test = .005.

Pancreatic, biliary, and colorectal cancers were more common primary cancer sites in Group A than in Group B (Table 2). In Group A, 17 patients (77%) conveyed the intention of continuing PC in the first interview with a physician of the palliative care team, compared with 4 patients (13%) in Group B (Table 3). The patients in Group B stopped PC a median of 43 days earlier than did the patients in Group A (Table 1). The patients in Group B decided to switch to best supportive care a median of 43 days earlier than did the patients in Group A (Table 1).

Retrospectively, the objective timing of progressive disease according to the radiological findings or changes in tumor markers and the timing of cessation of PC was not significant for the patients in Group A (Table 1). However, 10 patients (45%) in Group A continued PC after the evaluation that their cancer was progressive.

Patients in Group B, who were referred to CMH from TMCs, were interviewed by a physician of the palliative care team at the first visit. Therefore, the time interval between the first visit to CMH and death and that between referral to the palliative care team of CMH and death was equal for patients in Group B. The time interval between referral to the palliative care team of CMH and death was not significantly different between Group A and Group B patients (Table 1).

We performed subgroup analyses to exclude the difference in primary cancer sites between the groups. We extracted patients with pancreatic, biliary, colorectal, gastric, or esophageal cancers from both groups and defined them as Subgroup A (extracted from Group A) and Subgroup B (from Group B). We compared patient characteristics between Subgroup A and Subgroup B. Subgroup A also had the following significant findings in relation to Subgroup B: a larger proportion of patients willing to continue PC ($P < .0001$), a longer length of time between first visit to CMH and death ($P < .0001$), a shorter length of time between cessation of PC and death ($P < .0001$), and a shorter length of time between perception of supportive care and death ($P < .0001$), shown in Table 4.

TABLE 3 Comparison of patients' attitudes at the interview by a physician of palliative care team

Attitude	Group A (n = 22)	Group B (n = 30)	P value
Willing to continue PC when recommended supportive care, Yes:No	17:5	4:26	<.0001*
Preferred location of EoL when recommended supportive care, Home:Hospital:Unknown	15:7:0	19:9:2	.46†
Expression of fear of abandonment, Yes; n (%)	0 (0%)	4 (13.3%)	.12*

PC, palliative chemotherapy; EoL, end of life

*P value by Fisher's exact test. †P value by chi-square test.

Discussion

The primary cancer sites were different between Group A and Group B. One possible reason for that could be the lack of oncologists who specialize in gynecology, respiratory organs, and head and neck regions at CMH. However, without such oncologists, patients with gynecologic, lung, or head and neck cancers who needed supportive care near EoL required transfer to a local hospital. The patients in Group B visited several TMCs for treatment about 40 km (about 25 miles) away from their homes. The distance from the patients' homes to CMH was not significantly different between Group A and Group B. In addition, there was no significant difference between Group A and Group B with respect to the total length of hospital stay for symptom control, number of admissions for palliative care, and length of final hospital stay before death.

Patients' attitudes and wishes vary widely when faced with a life-threating or terminal illness; some patients are unwilling to undergo any treatment, whereas others are willing to undergo almost any treatment even if it has a small chance of being beneficial.[5,11] When the oncologist deems the continuation of PC to be futile, the patients cannot continue the treatment at TMC. They are forced

TABLE 4 Comparison of factors between Subgroup A and Subgroup B

Factor	Subgroup A (n = 21)	Subgroup B (n = 15)	P value
Median time interval between first visit to CMH and death, d (range)	247 (55-991)	60 (23-187)	.0001*
Median time interval between last chemotherapy and death, d (range)	50 (6-88)	89 (53-250)	.0004*
Median time interval between perception of supportive care and death, d (range)	32 (0-78)	90 (36-199)	<.0001*
Willing to continue anticancer therapy when recommended supportive care, Yes:No	17:4	4:11	.0019†

CMH, Chichibu Municipal Hospital

*P value by Mann-Whitney test. †P value by Fisher exact test.

to change the location of care, which may lead to them to express fears of abandonment, as seen in the Group B patients. To minimize this fear, oncologists must consider how to change the location of palliative care near the residence of patients or their family when PC becomes futile.

Oncologists at the previous medical institutions discussed the cessation of PC with the patients in Group B. Thus, few patients were willing to continue PC at the time of interview at CMH. However, many patients in Group A hoped to continue PC when referred to our palliative care team. Patient-related factors that may contribute to patients receiving futile PC at EoL include the personality traits of the patient and/or the family in not wanting to give up the hope of cure.[12] The physicians at our relatively small local hospital could meet these patients' expectations and would not want to disappoint them. Retrospectively, according to the data regarding the radiological findings or changes in tumor markers, 10 patients (45%) in Group A continued PC after the evaluation that their cancer was progressive. Although oncologists recognized disease progression in the patients in Group A, they continued PC for these patients to give them hope. An independent factor correlated with a shorter interval between the completion of PC and death was the presence of symptoms. Patients may believe that the outcomes of PC may be overly optimistic and PC is the only way to palliate their symptom because the tumor evokes the symptom.[13-15] Oncologists should tell their patients that PC is not the only way to eliminate symptoms and that its efficacy is limited if their general condition is poor.[16]

Although talking to patients and their families about cessation of PC and supportive care is not easy, oncologists must inform patients and their families in advance about the timing of cessation and help them make important EoL decisions.[5,17,18] Patients have few opportunities to discuss their preferences about EoL care with physicians throughout the course of their disease.[19] Ideally, oncologists should start PC with informed patient consent to the fact that PC is not for cure and that patients need to be referred to palliative care units at the same time as they receive PC. However, because data have shown that 19.6% of patients start PC without having been given information about palliative care units, this has not yet been achieved in clinical practice.[20] This is because physicians do not yet have sufficient data to enable them to decide whether they should stop PC or recommend hospice admission.[16]

Some limitations to this study need to be considered. First, our study was confined to a single institution within the specific subset of patients with incurable cancer and a limited number of oncologists at CMH. In particular, because of the small number of patients who received anticancer therapy only at CMH throughout the course of the disease, we cannot generalize our findings to other settings. However, Subgroup A showed a significantly shorter length of time between cessation of anticancer therapy and death, and a significantly shorter length of time between perception of supportive care and death after performing analyses to correct for the small sample size. Second, this study was retrospective in design; therefore, the findings may not be fully validated. To obtain more accurate data regarding EoL care, prospective cohort studies are needed to identify terminally ill patients and subsequently follow them until death.

It is assumed that the patients in Group B had been able to have an appropriate discussion with their oncologists about stopping PC before they transferred to CMH. We did not examine how many of the patients who had received anticancer therapy at TMCs did not transfer to CMH for supportive care and eventually died at the TMCs. Those patients may well be the patients who were more likely to continue PC until close to death. Therefore, we assumed that it would be easier for oncologists at a local hospital to discuss PC with patients who transferred there from a TMC after cessation of PC because the patients

would already have discussed the matter with the TMC oncologists before they transferred.

In conclusion, patients transferred to a local hospital from TMCs after cessation of anticancer therapy (Group B) stopped PC a median of 43 days earlier than those receiving therapy only in a local hospital (Group A). Four patients in Group B expressed fear of abandonment over the course of their disease, whereas no patient in Group A expressed similar fears. Change in the hospital where the patients are given supportive care may provide patients an opportunity to cease futile PC at an appropriate time after discussion with their oncologists. When changing a hospital, few patients expect the continuation of PC; however, the physician needs to consider the fear of abandonment of such patients.

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Full paper

Tris-hydroxymethyl-aminomethane enhances capsaicin-induced intracellular Ca^{2+} influx through transient receptor potential V1 (TRPV1) channels

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ABSTRACT

Non-selective transient receptor potential vanilloid (TRPV) cation channels are activated by various insults, including exposure to heat, acidity, and the compound capsaicin, resulting in sensations of pain in the skin, visceral organs, and oral cavity. Recently, TRPV1 activation was also demonstrated in response to basic pH elicited by ammonia and intracellular alkalization. Tris-hydroxymethyl aminomethane (THAM) is widely used as an alkalizing agent; however, the effects of THAM on TRPV1 channels have not been defined. In this study, we characterized the effects of THAM-induced TRPV1 channel activation in baby hamster kidney cells expressing human TRPV1 (hTRPV1) and the Ca^{2+}-sensitive fluorescent sensor GCaMP2 by real-time confocal microscopy. Notably, both capsaicin (1 μM) and pH 6.5 buffer elicited steep increases in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), while treatment with THAM (pH 8.5) alone had no effect. However, treatment with THAM (pH 8.5) following capsaicin application elicited a profound, long-lasting increase in $[Ca^{2+}]_i$ that was completely inhibited by the TRPV1 antagonist capsazepine. Taken together, these results suggest that hTRPV1 pre-activation is required to provoke enhanced, THAM-induced $[Ca^{2+}]_i$ increases, which could be a mechanism underlying pain induced by basic pH.

1. Introduction

Transient receptor potential (TRP) channels, including the TRP canonical (TRPC), TRP vanilloid (TRPV), TRP melastatin (TRPM), TRP mucolipin (TRPML), and TRP ankyrin (TRPA) subfamilies, are composed of four channel proteins that form a central pore through which cations such as Ca^{2+} and Na^+ can pass [1–3]. The first TRP channel cloned, TRPV1, is activated by several insults, including exposure to heat, acidity, and capsaicin, resulting in sensations of pain in the skin, visceral organs, and oral cavity [4–6]. In rat dorsal-root ganglion cells, acidic conditions can induce a persistent membrane potential current due to the inward flux of Na^+ and Ca^{2+} ions [6]; however, recent evidence indicates that TRPV1 can be activated by both acidic and basic pH [7].

Tris-hydroxymethyl aminomethane (THAM; brand name Trometamol) is an alkalizing agent that may be preferable to sodium bicarbonate because it acts as a hydrogen ion acceptor, thereby reducing CO_2 concentrations in the blood [8–10]. Ammonia and intracellular alkalization activate TRPV1 through a mechanism involving a cytoplasmic histidine residue [1–6]. THAM is widely

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used clinically to reverse acidosis [8–10]; however, the effects of THAM on TRPV1 channels have not yet been described.

In this study, we sought to characterize the direct effects of THAM on TRPV1 channel activity in an *in vitro* experimental system. To this end, baby hamster kidney (BHK) cells expressing human TRPV1 channels (hTRPV1) and the Ca^{2+}-sensitive fluorescent sensor GCaMP2 were stimulated with receptor agonists, and the resulting intracellular Ca^{2+} ($[Ca^{2+}]_i$) signals were then measured by real-time confocal microscopy [11–13].

2. Methods

2.1. Construction and expression of plasmids and chemicals

cDNA encoding full-length human TRPV1 was kindly provided by Dr. M. Tominaga (Division of Cell Signaling, Okazaki Institute for Integrative Bioscience, National Institutes of Natural Sciences, Okazaki). TRPV1 cDNA was subcloned into the expression vector pCI-neo (Promega, Madison, WI, USA). The pN1-GCaMP2 plasmid encoding the intracellular calcium sensor GCaMP2 was kindly gifted by Dr. J. Nakai (Saitama University Brain Science Institute, Saitama). Capsaicin and THAM were obtained from Sigma (St. Louis, MO, USA). Other chemicals were purchased from Nacalai Tesque (Kyoto).

2.2. Cell culture and transfection

BHK cells were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, penicillin (100 U/mL), and streptomycin (100 mg/mL) at 37 °C in a humidified atmosphere of 95% air and 5% CO_2. For Ca^{2+}-imaging, cells were seeded at a density of 6×10^4 cells per 35-mm (φ12-mm glass-bottomed) culture dish (WillCo Wells B.V., Amsterdam, Netherlands). Cells were transfected with 0.3 μg cDNA encoding hTRPV1 and 0.1 μg GCaMP2, using the Effectene transfection reagent (Qiagen, Tokyo). Assays were performed at approximately 24–36 h post-transfection.

2.3. Ca^{2+}-imaging assay

Ca^{2+} imaging was performed with BHK cells co-expressing TRPV1 using the Ca^{2+} sensor GCaMP2 [11–13]. The culture medium was discarded and the cells were washed twice with HEPES buffer (10 mM HEPES, 140 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, and 10 mM D-glucose, pH 7.4). The HEPES buffer was exchanged with test solution containing capsaicin and/or THAM (pH 8.5) and HEPES (pH 8.5), using a perfusion system. When using buffer at pH 6.0, we used Krebs-Ringer Phosphate (KRP)-buffered saline (pH 6.0). The fluorescence of GCaMP2 was continuously recorded at 510 nm to measure the fluorescence intensity in each whole cell. Ca^{2+} imaging was performed on a Meta 510 confocal microscope (Zeiss Japan, Tokyo). Data were acquired and analyzed with LSM510 META software (Carl Zeiss, Jena, Germany) and expressed as the fluorescence intensity (510 nm) before and after test solution exposure.

2.4. Capsaicin treatment

BHK cells expressing human TRPV1 were treated with 1 μM capsaicin for 30 s, washed for 10 min, and analyzed to confirm the expression status of both TRPV1 and GCaMP2. Test compounds were added in the presence of capsaicin, low pH buffer, high pH buffer, or THAM at various concentrations.

2.5. Statistical analysis

Data were analyzed using Prism 6 (GraphPad Software, San Diego, CA, USA). The Mann–Whitney test was used to compare the data between 2 groups, and non-parametric testing with Kruskal–Wallis one-way analysis of variance was used for multiple comparisons of control and treated groups.

3. Results

3.1. Real-time Ca^{2+} imaging-system optimization

Slight, but significant, green-fluorescent staining was observed in unstimulated hTRPV1/GCaMP2-expressing BHK cells. The fluorescent staining rapidly increased to a strong signal once stimulated with 1 μM capsaicin, implicative of an increase in $[Ca^{2+}]_i$, and quickly returned to basal levels (Fig. 1A). As expected, in the cells expressing hTRPV1/GCaMP2, KRP-buffered saline (pH 6.0) elicited increases in $[Ca^{2+}]_i$, as shown in Fig. 1B. Strong signaling elicited with 1 μM capsaicin or low-pH (6.0) KRP was not observed in BHK cells that expressed GCaMP2, but not TRPV1 (Fig. 1B).

To optimize the capsaicin concentration, we examined a range of capsaicin concentrations from 1 pM to 10 μM and observed robust peaks at 1 μM; however, significant increases in $[Ca^{2+}]_i$ were detected at a minimal concentration of 1 nM (data not shown). Based on these results, we used 1 μM capsaicin for the remaining studies. Both the capsaicin-induced and low-pH (6.0)-induced increases in $[Ca^{2+}]_i$ were completely inhibited when the hTRPV1 inhibitor capsazepine (10 μM) was added (Fig. 1C), consistent with previous findings [1–6].

In addition, a previous study showed that alkalization (high pH) was also sufficient to elicit TRPV1 activation [7]. Based on those findings, we examined the effect of high pH on hTRPV1 by adding HEPES (pH 8.5) or THAM (pH 8.5) at 0.3 mM, a concentration used clinically to treat acidosis [8, 10]. As shown in Fig. 1D, both HEPES and THAM increased $[Ca^{2+}]_i$ but not significantly. Moreover, treatment with 0.3 mM THAM at a higher pH (9.0) still failed to elicit any effects (data not shown).

3.2. Enhanced capsaicin-induced Ca^{2+} influx by THAM

BHK cells were exposed to 1 μM capsaicin for 30 s, followed by 0.3 mM THAM (pH 8.5) for 60 s, as shown in the inset of Fig. 2A. We observed a profound increase in $[Ca^{2+}]_i$, which persisted for >20 min (Fig. 2A).

Interestingly, the $[Ca^{2+}]_i$ increase was dependent on the timing of THAM application following capsaicin exposure. For example, while the simultaneous application of capsaicin with THAM did not induce a secondary increase in $[Ca^{2+}]_i$, treatment with THAM 30 s or 60 s after treatment with capsaicin elicited a profound secondary phase of $[Ca^{2+}]_i$ increases. However, a significant increase in $[Ca^{2+}]_i$ was no longer observed when THAM was added to BHK cells 90 s after capsaicin exposure (Fig. 2B).

Furthermore, when BHK cells were incubated simultaneously with the hTRPV1 inhibitor capsazepine (10 μM) and capsaicin, both capsaicin- and capsaicin/THAM-induced $[Ca^{2+}]_i$ increases were completely inhibited, regardless of the timing of the dosage (Fig. 2C, E). When capsazepine was added after capsaicin application, the elevation of $[Ca^{2+}]_i$ induced by THAM (Fig. 2A) was completely inhibited (Fig. 2D, E), indicating that opened TRPV1 channels are involved in THAM-induced $[Ca^{2+}]_i$ increases.

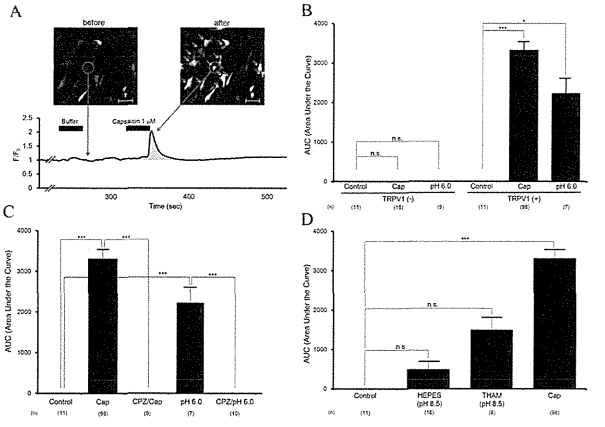

Fig. 1. Effects of compounds or buffers on changes in the intracellular concentration of Ca^{2+} ($[Ca^{2+}]_i$) in BHK cells expressing hTRPV1 and GCaMP2. (A) A typical tracing showing hTRPV1 activation induced by 1 μM capsaicin in cells expressing hTRPV1. (B) The effects of 1 μM capsaicin and KRP (pH 6.0) on the $[Ca^{2+}]_i$ in BHK cells with or without hTRPV1 expression. (C) The effects of 1 μM capsaicin and KRP (pH 6.0) on the $[Ca^{2+}]_i$ with or without 10 μM capsazepine. (D) The effects of HEPES (pH 8.5) and 0.3 mM THAM (pH 8.5) on the $[Ca^{2+}]_i$ in BHK cells expressing hTRPV1. The data shown are the mean ± SEM. $^*p < 0.05$; $^{***}p < 0.001$; Cap, capsaicin; CPZ, capsazepine; n.s., not significant; n, number of experiments.

3.3. Enhanced Ca^{2+} influx is capsaicin/THAM-specific

Acidification itself is reported to activate TRPV1 [5]. We showed here that KRP-buffered saline (pH 6.0) induced a significant increase in $[Ca^{2+}]_i$, whereas THAM (pH 8.5) had no significant effect (Fig. 1C). In contrast to the results observed following capsaicin treatment, THAM added simultaneously, or at 30, 60, or 90 s after low-pH buffer application failed to induce significant increases in $[Ca^{2+}]_i$ (Fig. 3).

This effect was THAM-specific, as no additional increase in $[Ca^{2+}]_i$ was observed when HEPES (pH 8.5), instead of THAM (pH 8.5), was added simultaneously or at 30, 60, or 90 s after capsaicin application (Fig. 4).

Moreover, we reversed the order of treatment from that shown in Fig. 2A and B, and examined the effects of THAM (pH 8.5) simultaneously or at 30, 60, or 90 s after application of capsaicin. In contrast to the data shown in Fig. 2B, THAM failed to enhance $[Ca^{2+}]_i$ when applied prior to capsaicin (Fig. 5).

4. Discussion

TRPV1 is activated by a variety of noxious stimuli, including the exposure to capsaicin, heat, low pH, and alkalization [1–6]. Here, we found that the alkalizing agent THAM (pH 8.5) potentiated TRPV1 activity if TRPV1 was pre-activated by capsaicin. Moreover, we found that low pH (~6.0) caused a significant and rapid increase in $[Ca^{2+}]_i$, consistent with previous findings [14]. We also demonstrated that treatment with THAM or HEPES at pH 8.5 did not independently increase $[Ca^{2+}]_i$; however, THAM (pH 8.5) strengthened and prolonged the capsaicin-induced increase in $[Ca^{2+}]_i$. This effect was time-dependent, as the $[Ca^{2+}]_i$ increase was only enhanced when THAM was added 30 or 60 s after capsaicin application, but not when added simultaneously or 90 s after stimulation. Further, the effect of THAM appeared to depend upon the "open-state" of TRPV1 because the THAM-induced increase in $[Ca^{2+}]_i$ was inhibited by capsazepine just after application of capsaicin (Fig. 2D). The precise mechanisms underlying this enhancement are presently unknown; however, we suggest that capsaicin-induced Ca^{2+} influx through TRPV1 channels terminates within 60 s because of pore closure. Accordingly, we did not observe a THAM-induced increase in $[Ca^{2+}]_i$ 90 s after capsaicin application since the TRPV1 channel was presumably closed. Furthermore, the simultaneous application of THAM and capsaicin failed to enhance Ca^{2+} influx, suggesting that the TRPV1 channel pore must be pre-opened by capsaicin for THAM to potentiate its activation.

In our study, THAM or HEPES buffer at pH 8.5 did not independently activate TRPV1, indicating that a high pH alone was insufficient to activate TRPV1 channels. However, combination treatment with THAM and capsaicin caused persistent increases in $[Ca^{2+}]_i$, most likely because THAM entered the cytosol through the capsaicin-activated TRPV1 channels. Thus, we theorize that

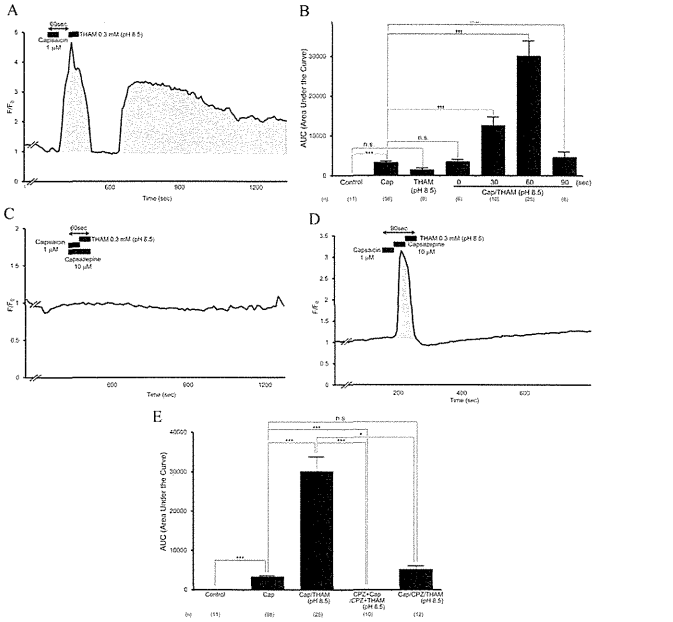

Fig. 2. Enhanced TRPV1 channel activity by THAM following the application of capsaicin. (A) Increase in $[Ca^{2+}]_i$ following stimulation with 1 μM capsaicin for 30 s followed by 0.3 mM THAM (pH 8.5) for 30 s. The time between capsaicin and THAM applications was 30 s. (B) Time-dependent effects of THAM application after capsaicin application. $[Ca^{2+}]_i$ data are expressed as the area under the curve (AUC) and are shown as the mean ± SEM. (C) Capsazepine (10 μM)-dependent inhibition of increased $[Ca^{2+}]_i$ after a 30 s stimulation with capsaicin (1 μM) and a subsequent 30 s stimulation with 0.3 mM THAM (pH 8.5). (D) Calcium influx following sequential 30 s stimulations with 1 μM capsaicin, 10 μM capsazepine, and 0.3 mM THAM (pH 8.5). (E) Effects of capsazepine on the capsaicin/THAM-induced increase in $[Ca^{2+}]_i$ in cells expressing hTRPV1. Data are expressed as the AUC of $[Ca^{2+}]_i$ and are shown as the mean ± SEM. $^*p < 0.05$; $^{***}p < 0.001$ vs. control; $^{\#\#\#}p < 0.001$ vs. 1 μM capsaicin; CPZ, capsazepine; n.s., not significant; n, number of experiments.

cytosolic THAM potentially binds to intracellular residues of TRPV1 that mediate TRPV1 activation by intracellular alkalization [7].

Previous data have shown that TRPV1 is activated by basic pH and have suggested that alkalization agents, such as ammonia, elicit a distinct, pungent sensation in the nose and airways, causing mucous membrane irritation that can develop into acute pneumonitis and chronic bronchitis with chronic exposure [15]. Our results showed that, although THAM (pH 8.5) alone did not elicit marked $[Ca^{2+}]_i$ increases in hTRPV1-expressing BHK cells, it did cause a robust and persistent increase in $[Ca^{2+}]_i$ in cells with pre-activated hTRPV1 channels that were opened by the noxious stimulus capsaicin. While ammonia can permeate cell membranes and activate TRPV1, THAM is likely hard to enter the cells because of its size and positive polarity [6]. The physiological significance of this phenomenon is unclear at present; however, we postulate that THAM causes a noxious sensation if TRPV1 is pre-activated by capsaicin, but not at a low pH (Figs. 2 and 3).

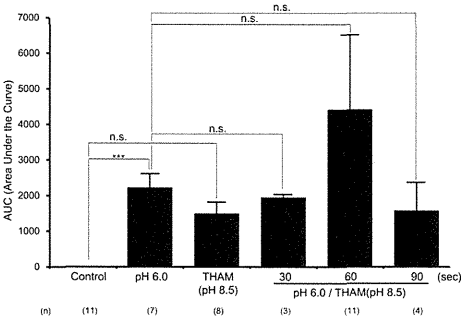

Fig. 3. Effects of varying the timing of THAM application following KRP (pH 6.0) buffer treatment. The data shown are expressed as the area under the curve (AUC) of $[Ca^{2+}]_i$ and are shown as the mean ± SEM. $^{***}p < 0.001$ vs. control; n.s., not significant; n, number of experiments.

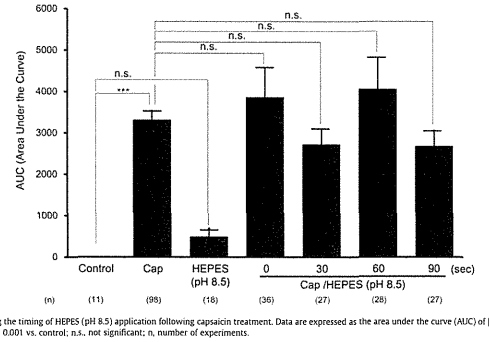

Fig. 4. Effects of varying the timing of HEPES (pH 8.5) application following capsaicin treatment. Data are expressed as the area under the curve (AUC) of $[Ca^{2+}]_i$ and are shown as the mean ± SEM. $^{***}p < 0.001$ vs. control; n.s., not significant; n, number of experiments.

Some findings have suggested that THAM may effectively compensate for acidosis, ameliorate the deleterious effects of prolonged hyperventilation, and may be beneficial in intracranial pressure control [16]. Previously, it was concluded that THAM administered at 0.55 mmol/(kg·h) to acute lung-injury patients with acidosis was associated with significantly increased arterial pH and base deficits, and triggered a reduction in arterial carbon dioxide tension that could not be fully accounted for by ventilation [8].

Several physiological conditions give rise to alkalinity, some of which are associated with pain sensations. A previous report demonstrated that rabbits infused with 0.3 M THAM showed necrosis around the site of infusion into the marginal ear vein [17]. In addition, respiratory alkalosis due to hyperventilation can cause a tingling sensation in the extremities and lower peripheral nerve thresholds [18]. It has also been suggested that alkaline pH causes pain sensation via TRPA1 activation and may provide a molecular explanation for some human alkaline pH-related sensory disorders

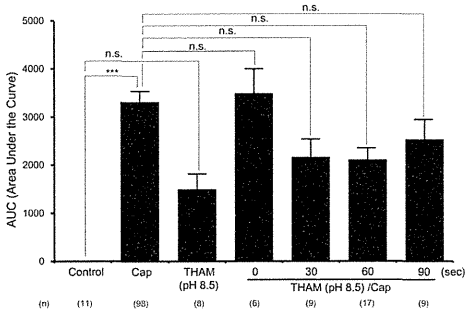

Fig. 5. Effects of varying the timing of capsaicin application following THAM (pH 8.5) treatment. Data are expressed as the area under the curve (AUC) of $[Ca^{2+}]_i$ and are shown as the mean ± SEM. ***$p < 0.001$ vs. control; n.s., not significant; n, number of experiments.

[19]. However, the role of TRPV1 in such disorders has yet to be reported.

Our data showed that THAM prolonged TRPV1 channel activity if the channels were pre-activated. Although the significance of prolonged TRPV1 channel activation is unclear, our results suggest that THAM may cause pain sensations in some circumstances. Thus, it is important to determine how THAM can be used more effectively and promptly in treating pathophysiological conditions involving TRPV1 channel pre-activation.

Conflict of interest

None.

Acknowledgements

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A national profile of the impact of parental cancer on their children in Japan

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ABSTRACT

Objective: Dependent children under the age of 18 are particularly vulnerable to the stress of parental death from cancer or of having a parent diagnosed and treated for the disease. More and more Japanese couples are postponing parenthood, which increases their chances of developing cancer while they still have a dependent child. However, the problem has not received enough attention from healthcare professionals and policy-makers because the extent and breadth of the problem has never been examined in the Japanese population. Therefore, we aimed to estimate the nationwide incidence of cancer patients who have children under the age of 18 years, as well as the incidence of children who have a parent diagnosed with cancer in Japan.
Study design: We calculated the proportion of patients who have children stratified by age, gender and cancer type using electronic medical records of cancer patients (20–59 years old) admitted to the National Cancer Center Hospital (NCCH) for the first time between January 2009 and December 2013. We projected these estimates onto the Japanese population using 2010 population-based cancer registry data, and repeated the projection using 2011 hospital-based cancer registry data so that estimates of patients receiving care at Designated Cancer Care (DCC) hospitals could be obtained.
Results: We found that an estimated 56,143 cancer patients who have 87,017 dependent children are diagnosed with cancer every year in Japan. The proportion of children in Japan who had a parent newly diagnosed with cancer in 2010 was approximately 0.38%. We estimated that in 2011 there were on average about 82 cancer patients with minor children and 128 minor children who have at least one parent diagnosed with cancer in every DCC hospital in Japan.
Conclusion: Parental cancer is common. We have identified that many adults diagnosed with cancer have the double burden of coping with the diagnosis and treatment as well as supporting their children through this experience. Additional data on socioeconomic characteristics and needs assessment of these patients are required to understand how best to help children and families cope with cancer.

1. Background

A cancer diagnosis often has a significant negative impact on the lives of patients and their families [1]. It influences the psychosocial and emotional wellbeing of minor children. [2] However, cancer among parents who have dependent children is becoming an increasing problem in many developed countries as more people postpone parenthood [3]. The lifetime risk of cancer

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in Japan is stunningly high compared to that in other countries – 56% for males and 43% for females [4] (US: 43% and 38% [5], UK: 44% and 40% [6], respectively) – which means that a greater number of individuals will become parents at an age where cancer risks are high and their children are still young and dependent. Even if these patients constitute a small group of cancer patients, it is nonetheless a growing problem that deserves special attention because of its severe and long-lasting impact on both the child and the patient.

In spite of this clear need for more attention, no study has ever captured the severity of the issue in Japan. In Norway, approximately 4% of children aged 0–25 years have or have had parents diagnosed with cancer, which corresponds to a population prevalence of 1.4% [7]. At least 18% of cancer patients in the United States have minor children. [8] The purpose of this study was to obtain national estimates for the number and proportion of cancer patients who have dependent minor children, as well as the national estimates for the number of children with a cancer parent in Japan.

2. Methods

2.1. Data sources

Using the NCCH's electronic medical records (EMRs), we identified patients between the ages of 20 and 59 who were admitted to the National Cancer Center Hospital (NCCH) for the first time between January 2009 and December 2013. We extracted their age at their first hospital admission, gender, and the number, age, and gender of their children, and excluded patients who could not be identified within the hospital-based cancer registry (HBCR) database which contained their International Classification of Diseases Oncology, 3rd edition (ICD-O-3) topography and morphology codes.

We used the 2010 population-based cancer registry (PBCR) and the 2011 HBCR data to make inferences for the burden of cancer among patients with children for the total Japanese population and also for patients who received care at a designated cancer care (DCC) hospital in Japan. The PBCR collects cancer surveillance data from 35 prefectures (out of a total of 47) that have a case reporting system for newly diagnosed and treated cancer patients from hospitals and clinics within their prefecture. Because case reporting is not mandatory, PBCR data do not capture all cancer incidence in Japan [9]. The HBCR, on the other hand, is a compulsory cancer incidence reporting system for DCC hospitals in Japan. In 2011, there were 395 hospitals that were designated as DCC by the Ministry of Health, Labor, and Welfare, to play a major role in the prevention, diagnosis, and treatment of cancer for most cancer patients. Although there are non-designated hospitals that also care for cancer patients, they are not required to submit their surveillance data to the HBCR.

2.2. Analyses

We calculated the number and proportion of cancer patients with dependent children under the age of 18, stratified by the patient's gender, age group (ages 20–29, 30–39, 40–49 and 50–59) and cancer types from data obtained from NCCH's EMRs. We also counted the total number of children among all cancer parents according to the child's age group (ages 0–6, 7–12, 13–15, and 16–18) and gender. Data were analyzed using Stata 13.1 (Stata Corporation, College Station, TX, USA).

We made inferences for the number of cancer patients who have dependent children in Japan, as well as the number of children with a parent diagnosed with cancer in a year, by multiplying them by the incidence of cancer for patients in the same strata of gender, age group, and cancer type as the PBCR. We also estimated the number of cancer parents and the number of children who have a parent with cancer who received care at DCC hospitals in Japan.

3. Results

Among 12,399 men and 10,786 women who were admitted to the NCCH for the first time between January 2009 and December

Table 1
The distribution of cancer patients who are parents between the ages of 20 and 59 at the time of first admission to the National Cancer Center Hospital between 2009 and 2013.

	Male		Female		Total	
Age of patients	N of patients (% of patients with minors)	Average N of children	N of patients (% of patients with minors)	Average N of children	N of patients (% of patients with minors)	Average N of children
20–29	142 3.5%	1.2	136 11.8%	1.6	278 7.6%	1.5
30–39	389 31.1%	1.7	555 34.2%	1.7	944 32.9%	1.7
40–49	726 46.4%	1.7	1310 41.3%	1.6	2036 43.1%	1.7
50–59	1705 16.8%	1.4	1727 8.9%	1.3	3432 12.8%	1.3
Total	2962 25.3%	1.6	3728 24.1%	1.6	6690 24.7%	1.6

Common cancer types	Male					Female					
	N of patients with minors				Total N of patients with minors	Common cancer types	N of patients with minors				Total N of patients with minors
	Patients' age						Patients' age				
	20–29	30–39	40–49	50–59			20–29	30–39	40–49	50–59	
Gastric	0	15	48	54	117 (15.6%)	Breast	2	61	241	57	361 (40.1%)
Lung	0	13	41	45	99 (13.2%)	Uterus	0	18	61	15	94 (10.4%)
Colorectal	0	7	44	37	88 (11.7%)	Gastric	2	12	44	9	67 (7.4%)
Sarcoma	0	23	31	13	67 (8.9%)	Sarcoma	6	23	31	5	65 (7.2%)
Lymphoma	1	18	27	16	62 (8.3%)	Colorectal	2	11	31	14	58 (6.4%)

2013, we identified 8412 patients between the ages of 20 and 59. We excluded 1295 patients whose data could not be linked to HBCR data, and further excluded 427 patients with in-situ carcinoma because these patients were not registered within the PBCR. This left 2962 males (44.3%) and 3731 females (55.7%) in the analyses.

We identified 2593 minor children among 1650 cancer patients in our study. Roughly a quarter of both male (25.3%) and female (24.1%) patients had at least one minor child (Table 1). The average age of fathers who had cancer was 3 years older than mothers with cancer (mean: 46.6 versus 43.7 years, SD: 7.0 versus 6.1 years, $P < 0.05$). The average number of minor children for a cancer patient in our study was highest among patients in their 30s and 40s. The most common cancer types for fathers with children were gastric (15.6%), lung (13.2%), and colorectal (11.7%) cancers, and for the mothers breast (40.1%), uterus (10.4%), gastric (7.4%) cancers (Table 1). The average age of the children was 11.2 years (SD: 5.2). The proportion of children whose parent had cancer tended to increase as the child's age increased (Fig. 1).

Using incidence rates of cancer patients from the PBCR and HBCR within the same strata of age, gender, and cancer type, we estimated that 56,143 patients with 87,017 children were diagnosed with cancer in Japan in 2010, and among these 32,679 cancer patients with 50,752 minor children received care at DCC hospitals (Table 2).

4. Discussion

Our study showed that an estimated 56,143 cancer patients who had 87,017 dependent children were diagnosed with cancer in Japan in a year. Given that the total population of minors in Japan was 22,780,000 in 2010 [10], the proportion of children with a parent diagnosed with cancer was approximately 0.38%. The most common age group for cancer patients with children was 40–49 years old, and the most common cancer type was breast cancer. The number of children with parental cancer increased as the child's age increased.

Table 2
National estimates of the incidence of cancer patients with children and children with cancer parents projected from population-based and hospital-based cancer registry (PBCR and HBCR) data (per 1 year).

	Male		Female		Total	
Age of patients	PBCR	HBCR	PBCR	HBCR	PBCR	HBCR
20–29	66	78	310	291	377	369
30–39	1922	1417	5702	5196	7623	6613
40–49	9460	5210	18885	11121	28345	16331
50–59	13478	5910	6320	3456	19797	9366
Total	24926	12615	31217	20064	56143	32679

	Boys		Girls		Total	
Age of children	PBCR	HBCR	PBCR	HBCR	PBCR	HBCR
0–6	13591	7927	13625	7947	27216	15874
7–12	14598	8515	12685	7399	27283	15913
13–15	8625	5030	8759	5108	17383	10139
16–18	7886	4600	7249	4228	15135	8827
Total	44700	26071	42317	24681	87017	50752

PBCR, population-based cancer registry; HBCR, hospital-based cancer registry.

Prior study has shown that patients with invasive cancer who have dependent children tend to be more anxious, more likely to prefer aggressive treatment over palliative care, and more likely to have worse quality of life in their last weeks of life compared to patients without dependent children [11]. Adolescent teens who have a parent with cancer experience higher levels of emotional stress compared to their younger school-aged counterparts [12,13]. Gender, birth order and number of siblings, and single parenthood also may predict the risk of emotional problems in the child or adolescent [14]. Future research should investigate the background and specific needs of cancer patients and their children, so that healthcare providers and policy-makers can develop necessary support services for future patients and their children. Other countries have developed various programs and interventions to support children who have a parent with cancer. Support ranges from family sessions to parallel group sessions for children and

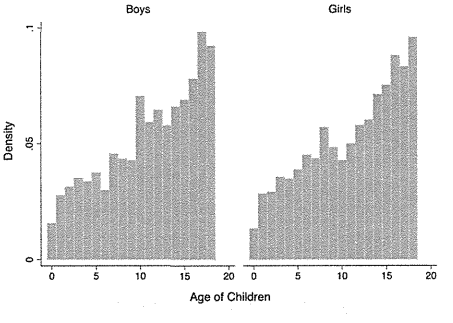

Fig. 1. The distribution of the ages of dependent children with a parent diagnosed with cancer in the National Cancer Center Hospital between 2009 and 2013.