質疑応答

Q1 Infusion reactionへの対応を教えてください。

Infusion reactionがみられたら，まずセツキシマブ投与を止めることが重要です。点滴をする際に必ずしも医師がいるとは限らないことを考えると，infusion reactionが起こる可能性があることを看護師にも情報共有し，注意喚起をすることが大切だと思います。

また，セツキシマブ投与を止めた後に使用する薬剤の指示などのマニュアルの作成をしておく，ステロイドを含んだ薬剤のセットを治療前に準備しておくなど，すぐに対応できるよう病院全体で共有するとよいと思います。

Q2 わが国でconcomitant boost法を用いた試験は唯一だと思うのですが，従来の通常分割に対して，局所制御の上乗せがあるのでしょうか。また，今回は強度変調放射線治療（IMRT）の装置ではなくて，従来の装置を使用されたのですか。

1日2回照射をすることの煩雑さなど種々の要素を考えると，IMRTで70Gy/33fractionsや70Gy/35fractionsの照射とさほどの差は出ない印象があります。実臨床ですべてconcomitant boost法で実施しないといけないとは思いません。Bonner試験に沿って行ったため1日2回照射を選んだのですが，装置は日本の水準を鑑みてIMRTではなく通常の3DRTで実施しました。

Q3 今回の試験はconcomitant boost法を用いて行われましたが，いま通常分割法が見直されていると個人的に思っています。今後，日本での照射法についてアドバイスをいただけますでしょうか（Ang先生に対して）。

Concomitant boost法はIMRTが普及する前に行われていた方法で，IMRTの普及とともに治療の迅速化と多分割のコンセプトを統合できるようになったため，現在はIMRT 70Gy/35fractions（7週間）を用いています。したがって，緻密なdose paintingによって正常組織への線量を低減できる照射を行うことで将来的にはIMRT 70Gy/30fractions（6週間）で完遂できるようになると思います（by Ang先生）。

JOHNS
特集●下咽頭癌はここまで治る●

QOL向上を目指して

放射線治療による有害事象軽減のための支持療法

全田貞幹*
Sadamoto ZENDA

● Key Words ●放射線治療，有害事象，粘膜炎，皮膚炎，支持療法●

はじめに

近年，進行下咽頭癌に対して喉頭温存を目的に化学放射線療法を選択する機会が多くなってきた。わが国における化学放射線療法ではその照射線量および抗癌薬の投与量は海外のそれに低く設定されている。一方毒性の頻度は同等もしくはそれ以上とされ，学会等では皮膚炎，口内炎・粘膜炎の出現による治療の休止や中止も多く報告されている。その原因として，人種差など患者側の問題を指摘する意見もあるが医療者側の問題として疼痛や皮膚炎などの対策を医師や看護師個人の判断に任せ，体系的な管理がうまくできていないことも考慮すべきである。

放射線治療は治療期間と抗腫瘍効果の関係[1]が指摘されており，安易に治療を休止することは治療成績の低下につながるためできるだけ避けなければならない。本稿では，各毒性に対して体系的な対策を講じることで予定通り治療を完遂することを目指すいくつかの支持療法について示し，その具体例について解説する。

Ⅰ．放射線治療中に起こる有害事象とその対策

有害事象の対策は大きく予防と対症に分けられ，それぞれの副作用についていずれかの方法をとるべきである。

1．口内炎・粘膜炎（図1）

口内炎・粘膜炎は下咽頭癌の放射線治療においては必発の副作用であるため，しっかりとした対策を立てればこれによる治療休止を最小限に抑えることができる。口内炎・粘膜炎の予防策については薬剤を用いた試験が検証されてきたが，予防することで治療効果に影響のある薬剤もあったため，現状臨床の現場では対症療法に専念することが勧められる。

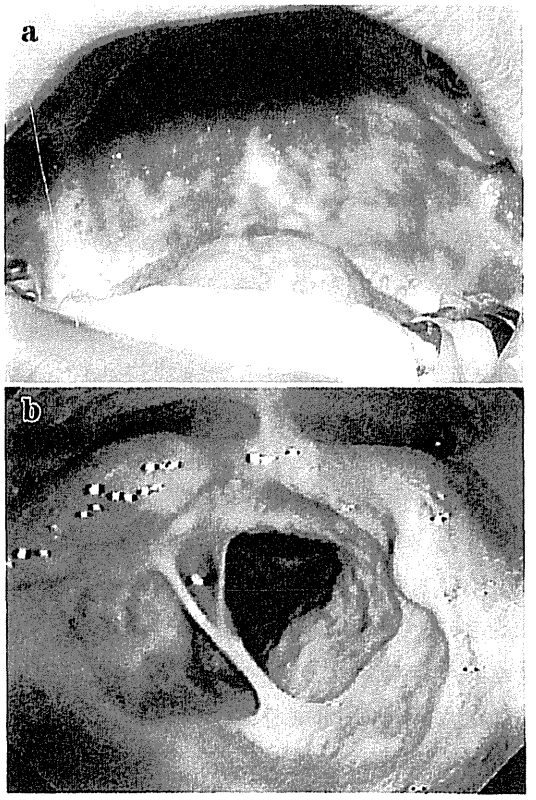

図1　口内炎（a）・粘膜炎（b）

本邦において他施設共同研究として疼痛管理に関する試験[2]が行われ，その結果が公表されている。その方法は“opioid based pain control program”（図2）と呼称され，確実な栄養・薬剤投与経路として胃瘻を造設し疼痛はモルヒネを主軸

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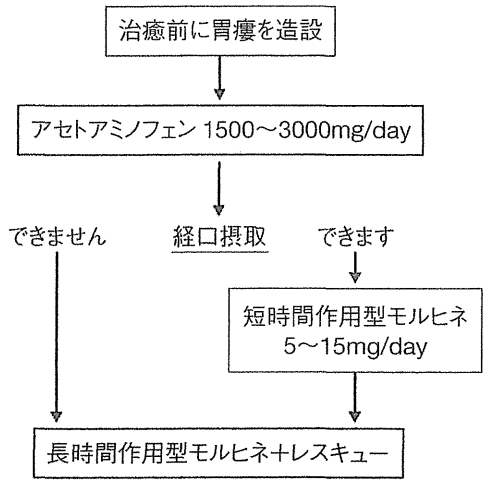

図 2　Opioid based pain control program

に管理していくというものであったが，この試験では放射線治療を予定外に中止した患者はわずか1例（0.9%）で休止率も12.7%（1週間以上の休止は0例）と治療完遂という点において優れた成績を報告している。

付随的なデータとして，化学放射線療法中にモルヒネが必要になる患者は約8割であり，使用するモルヒネの使用量の中央値は35 mg程度であった。NSAIDsはCDDPとの腎毒性で相乗効果が疑われるため，NSAIDsではなくモルヒネを使用するという点は理にかなっていると言える。

また，胃瘻に関するトラブルは治療中で4%程度と非常に低く，一方患者教育により退院して患者管理が可能になる割合は90%と非常に高かった。胃瘻についてはこの試験では治療前に造設している。海外では治療中に造設する施設もあり，各施設の事情にあったセッティングが必要と考える。

2．皮膚炎（図3）

皮膚炎も放射線治療を行っている患者には必発の副作用である。それ自体命に別状はないものの，管理をずさんにすると感染の引き金になったり，照射野に痕が残ってしまったりと患者のQOLに影響を及ぼす可能性が高いためしっかり対応する必要がある。皮膚炎の予防は現時点で有効なものはなく，対症療法に専念すべきである。

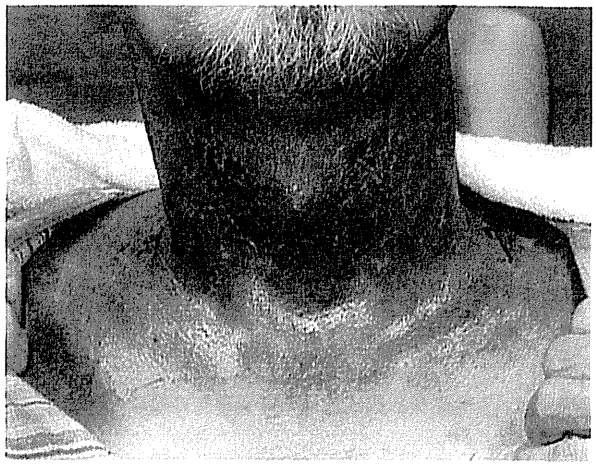

図 3　皮膚炎（グレード2）

皮膚炎管理の要則は，

1）照射野内の皮膚に対する刺激を避ける

2）清潔にする

3）保湿する

の3つである。

1）照射野内の皮膚に対する刺激を避ける

実臨床において皮膚炎予防を企図して照射早期から照射内に薬剤等を塗布することがあるが，その場合は物理的刺激による皮膚炎の増悪の可能性があることも念頭に置くべきである。

予防的な処置が皮膚炎軽減に寄与するというエビデンスはなく，また逆効果であると報告しているものもないため，予防的処置の有効性は学術的にはいまだ不明である。

2）清潔にする

皮膚炎の症状がだんだん強くなると患者やその家族はその部位にできるだけ触れないようにする傾向があり，その結果，照射野がやや不潔になってしまうことがある。Crustやガーゼの糸等を照射野に残しておくと感染の契機や創傷治癒遅延の原因となるため，洗浄した方がよい。

ヨードや過酸化水素水などで消毒すると組織が挫滅し，逆に創傷治癒が遅延するため消毒はしてはいけない。

3）保湿する

従来傷は乾燥させて治すとされてきたが，近年その発想は逆転し治癒した傷が乾燥することがわかってきた。湿性落屑は創傷治癒のために必要なサイトカインであり，これを拭き取って乾燥状態

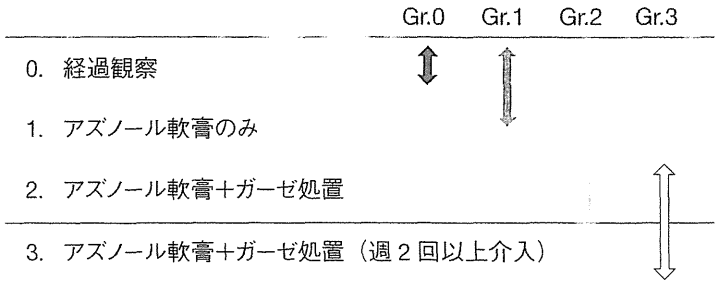

図 4　Dermatitis Control Program（DeCoP）

にすることは創傷治癒を遅延させる行為である。

傷を乾燥させるという方法は看護領域，一部の医師間でもまだ根強く残っているため，医師-看護師とよく連携し意思統一することが肝要である。

全田らは，上記の３つをプログラムに組み込んだ皮膚炎管理プログラム（Dermatitis Control Program：DeCoP）を開発し，前向きコホート試験[3]を行った（図 4）。

根治的（化学）放射線治療を受けた 113 例の患者を対象に DeCoP で皮膚炎処置を行った結果，皮膚炎 Gr.3 の発現はわずかに 9.7％と少なく，治療開始から２週間後には半数以上の患者に皮膚炎の回復が確認されたと報告している

ステロイド軟膏の使用については賛否両論ある[4,5]ところだが，ステロイドの有用性を示した臨床試験はなく，積極的な使用を勧める根拠は乏しい。しかしながらステロイドが無効であることを示したものもなく，長く慣例的に行われていることを考慮すると現時点では各施設の裁量に任せられるところである。

３．味覚障害

味覚障害については，栄養学や亜鉛の補正などさまざまな試みがなされているが，いずれも規模が小さく，決め手となるような研究はまだ成就していない。今後の取り組むべき課題と言える。

４．口内乾燥（唾液腺障害）

頭頸部の放射線治療を行った場合，口内乾燥は従来避けられない副作用であったが，近年薬剤や照射技術開発によるアプローチなど成果が出ているものもある。

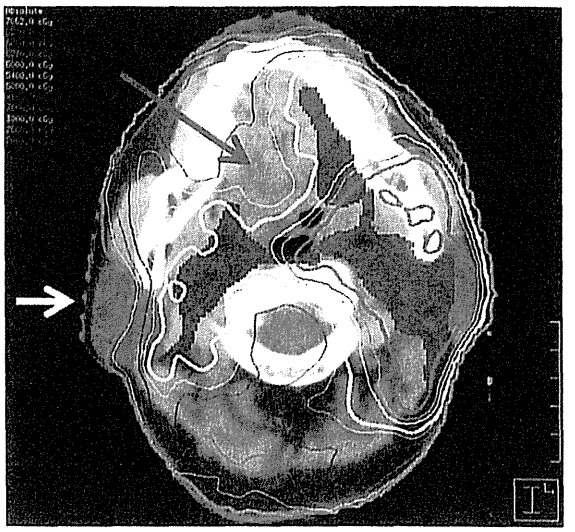

図 5　IMRT による重要臓器の遮蔽
IMRT を用いた右唾液腺の遮蔽。
赤矢印：口腔内の線量を低減している
白矢印：右唾液腺を遮蔽している

１）内服薬（ピロカルピン塩酸塩）

ピロカルピン（商品名：サラジェン）は元々シェーグレン症候群による口腔乾燥に用いられていた薬剤であるが，これを放射線治療による口内乾燥に応用し奏効している症例もある。

副作用として多汗，鼻炎，下痢，頻尿，頭痛，ほてり，嘔気，悪寒などがあり，投与の継続に関しては，奏効しているかどうかに加え上記の副作用の強さによっても判断が必要である。

２）IMRT（強度変調放射線治療）

海外では既にこの手法がスタンダードであるが，日本では頭頸部領域でまだ1～2割程度しか普及していない。

IMRTはその高度な照射技術で唾液腺自体を遮蔽することが可能[6]であり，最も効果的な口腔乾燥予防の手段である（**図5**）。

さいごに

強力な治療を行えば強い副作用が出ることはいわば当然のことであり，強力な治療と副作用対策はセットで考えなければ成立しない。逆に副作用を気にして本治療の強度を下げてしまうことは生存率の低下につながり，最終的には患者の不利益になりうる。新規の治療が開発されればそれに伴って対応する副作用処置を考えてしかるべきであり，そのようなバランス感覚も術者に求められるところである。

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Psycho-Oncology
Psycho-Oncology **22**: 2347–2353 (2013)
Published online 19 May 2013 in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.3300

Depressive symptoms after treatment in hepatocellular carcinoma survivors: prevalence, determinants, and impact on health-related quality of life

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Received: 20 January 2013
Revised: 17 April 2013
Accepted: 22 April 2013

Abstract

***Objective*: The purposes of this study were to investigate the prevalence and determinants of depressive symptoms among hepatocellular carcinoma (HCC) survivors and to evaluate the impact of depressive symptoms on health-related quality of life (HRQOL).**

***Methods*: A cross-sectional study was conducted on 128 consecutive patients attending an outpatient clinic in Japan 1 year or more after curative treatment. To assess depressive symptoms and HRQOL, the participants were asked to complete the Center for Epidemiologic Studies Depressive Symptoms Scale, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, and EORTC QLQ-HCC18, respectively. Multiple logistic regression models were used to identify factors associated with depressive symptoms. EORTC QLQ-C30 and EORTC QLQ-HCC18 scores were compared between participants with and without depressive symptoms.**

***Results*: The prevalence of depressive symptoms among the HCC survivors was 28.3%. The multiple logistic regression analysis revealed that the determinants of depressive symptoms included poor Karnofsky performance status (odds ratio [OR] = 4.59, 95% CI = 1.03–20.55, $p = 0.04$), poor liver function (OR = 3.22, 95% CI = 1.11–10.0, $p = 0.03$), living alone (OR = 6.87, 95% CI = 2.53–18.63, $p = 0.0002$), and unemployment (OR = 5.18, 95% CI = 1.73–15.54, $p = 0.003$). Survivors with depressive symptoms had poorer HRQOL in almost all domains compared with survivors with no depressive symptoms.**

***Conclusions*: This study suggests that after treatment, many HCC survivors experience depressive symptoms that are strongly associated with poorer HRQOL.**
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Introduction

Hepatocellular carcinoma (HCC) is a major health problem worldwide [1]. It is the sixth most common malignancy in the world, with more than half a million new cases annually [1]. The HCC 5-year survival rate after liver resection or liver transplantation has reached over 50% because of improvements in diagnosis and treatment, and the number of HCC survivors has increased [2]. The HCC recurrence rate is very high because of chronic hepatitis, which is the predominant risk factor for HCC in China, Western countries, and Japan [2,3]. Therefore, it is becoming increasingly important to preserve health-related quality of life (HRQOL) of HCC patients during their prolonged life span.

It is known that many cancer survivors experience a number of symptoms and posttreatment effects, including depressive symptoms [4]. Although depressive symptom is a symptom that occurs during the course of cancer, it persists for years after the completion of treatment, and it is one of the most frequent symptoms experienced by cancer survivors [4,5]. It has been suggested that depressive symptoms strongly affect HRQOL [4,6] and can lead to a shorter survival of cancer patients [7,8]. Fortunately, depressive symptoms are treatable. Numerous randomized controlled trials show that psychological distress, including depressive symptoms, can be alleviated by pharmacologic and nonpharmacologic interventions [9]. Therefore, it is particularly important, for cancer survivors, to implement routine depressive symptoms screening and provide appropriate care and treatment.

Although research interest in depressive symptoms among cancer survivors has increased in recent decades, there have been no studies investigating depressive symptoms among HCC survivors. Therefore, little is known about the prevalence and causes of depressive symptoms among HCC survivors, or the characteristics of those most at risk of developing depressive symptoms. This situation makes it difficult to manage the problem. Thus, the aims of this study were to estimate the prevalence of depressive symptoms in HCC survivors more than 1-year posttreatment, to identify factors associated

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with depressive symptoms, and to evaluate the impact of depressive symptoms on HRQOL.

Materials and methods

Data collection

We conducted a cross-sectional study of HCC survivors 1 year or more after HCC treatment (curative treatment). The HCC survivors were selected from patients who consecutively attended the Gastroenterology Outpatient Clinic of The University of Tokyo Hospital (a tertiary care teaching hospital). Patients went to see a doctor every 3 months to check for the recurrence of HCC. Patient medical records were reviewed prior to selecting potentially eligible patients. The eligibility criteria were as follows: (1) diagnosed with HCC more than 1 year prior to data collection and had curative treatment at The University of Tokyo Hospital; (2) able to communicate in Japanese; (3) able to participate in the study, as judged by an attending doctor; and (4) 20 years of age or older. Patients with evidence of metastatic or recurrent cancer, those with a history of other types of cancer, and those who were receiving cancer treatment were excluded from the study.

Data were collected after the patients' medical appointments from August 2008 to August 2009 by one of the investigators. Patients self-administered the questionnaires. Medical data were collected by reviewing the patients' medical care records. The investigator checked for absent responses after receiving the questionnaire and when possible, asked the patients to respond to missing items. The ethics committee of The University of Tokyo approved this study, and all participants provided their written informed consent.

Measurement of depressive symptoms

Depressive symptoms were measured using the Japanese version of the Center for Epidemiologic Studies Depressive Symptoms Scale (CES-D) [10]. The CES-D is a 20-item self-report questionnaire designed for the screening of depressive symptoms. Scores for each item are summed to give a range of total scores from 0 to 60. A higher score indicates a greater tendency toward depressive symptoms. A score of 16 points or higher suggests the presence of clinical depressive symptoms [10]. The reliability and validity of the Japanese version of the CES-D have been confirmed [10]. In the Japanese version, the cutoff value of 16 was also optimal, assessed by comparing the proportion of patients with CES-D score of 16 points or higher in a normal control group with that in a group of patients with mood disorders [10].

Measurement of health-related quality of life

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3.0) is a questionnaire for assessing HRQOL of cancer patients. The self-administered questionnaire includes a total of 30 items and includes six functioning scales: physical (five items), emotional (four items), role (two items), cognitive (two items), and social functioning (two items), as well as global health status (two items). The questionnaire also includes three symptom scales: vomiting (two items), fatigue (three items), and pain (two items). Six single items assess dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. The global health status items are rated from 1 (very poor) to 7 (excellent), and the remaining items are rated 1 (not at all) to 4 (very much). All item response scores were converted into 0–100 scores according to the EORTC scoring guidelines. Higher scores mean a better function or a worse symptom. The reliability and validity of the Japanese version of the EORTC QLQ-C30 have been confirmed [11].

The EORTC QLQ-HCC18 is an HCC-specific supplemental module developed to augment QLQ-C30 and to enhance the sensitivity and specificity of HCC-related QOL issues [12,13]. The self-administered questionnaire includes a total of 18 items and includes six multi-item scales: fatigue (three items), body image (two items), jaundice (two items), nutrition (five items), pain (two items), and fever (two items). Two single items assess sexual life and abdominal swelling. The items are rated 1 (not at all) to 4 (very much). The scales and items are linearly transformed to a 0–100 score, where 100 represents the worst status. The reliability and validity of the Japanese version of the EORTC QLQ-HCC18 have been confirmed [14].

Sociodemographic characteristics

The following sociodemographic information was collected from the self-administered questionnaire: gender, age, employment status, educational level, and cohabitation status.

Clinical characteristics

The following clinical information was collected from the patients' medical records: Karnofsky performance status (KPS), etiology of liver disease, comorbidity other than chronic liver disease, liver function (Child–Pugh grade), history of HCC recurrence after initial treatment, and time since treatment. Higher scores in KPS signify better performance status. We placed cutoff value at 80 points, where patients begin to feel difficulties in normal activity or work. Liver function becomes worse in alphabetical order of Child–Pugh grades A, B, and C.

Statistical analysis

Descriptive statistics are used to present the prevalence of depressive symptoms and the characteristics of the participants. The prevalence of depressive symptoms was

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DOI: 10.1002/pon

determined by calculating the proportion of patients exhibiting a score of 16 points or higher on the CES-D.

We used *t*-tests to compare the EORTC QLQ-C30 and EORTC QLQ-HCC18 domain scores between the HCC survivors with depressive symptoms and those with no depressive symptoms. The clinical relevance of the difference in the mean scores of HRQOL scales between groups was further measured by calculating the effect size using Cohen's *d* coefficient. As recommended [15], we considered *d* values less than 0.2, anything above 0.2 but less than 0.5, and anything at or above 0.5 as indicating small, moderate, and large effect sizes, respectively. Chi-squared tests, Fisher's exact tests, and *t*-tests were used to compare CES-D scores among sociodemographic and clinical variables, as appropriate. To identify the sociodemographic and clinical variables that were independently associated with depressive symptoms, multivariate logistic regression models were used. Variables with a p value of 0.2 or less were included in a backward variable selection. Odds ratios and 95% CIs were calculated for each variable in the final model. In all statistical tests, $p < 0.05$ (two-sided) was regarded as statistically significant. Statistical analyses were performed using SAS release 9.2 (SAS institute Inc., Cary NC, USA).

Results

Among 128 eligible patients, one refused to participate (because of a lack of time). Thus, data from 127 patients were included in this study, a response rate of 99.2%. There were no missing data at the item or scale level.

Table 1. Sociodemographic and clinical characteristics of the study subjects

Variable	n (%)
Male gender	81 (63.7)
Age (years)[a]	69.0 ± 8.4
Employed full time or part-time	50 (39.4)
Education	
≤12 years	83 (65.3)
Living with family or other adults	85 (66.9)
Karnofsky performance status	
80–100	113 (88.9)
Etiology of liver disease	
Hepatitis C virus	75 (59.0)
Hepatitis B virus	43 (33.9)
Comorbidity other than chronic liver disease	
Yes	83 (65.4)
Child–Pugh grade	
A	96 (75.5)
History of HCC recurrence after initial treatment	
Yes	87 (68.5)
Time since treatment (months)[a]	24.7 ± 18.5

Values are expressed as numbers (%) unless otherwise specified.
HCC, hepatocellular carcinoma.
[a]Data are expressed as mean (standard deviation). Higher Karnofsky performance scores signify better performance status. Liver function becomes worse with increasing Child–Pugh grades A, B, and C.

Sociodemographic and clinical characteristics of the study subjects

Table 1 presents the sociodemographic and clinical characteristics of the study subjects. Most patients were men (63.7%), had good performance status (88.9%), and had good liver function (75.5%). The mean age of survivors was 69.0 years (standard deviation [SD] = 8.4), and the average time since treatment was 24.7 months (SD = 18.5).

Characteristics of hepatocellular carcinoma survivors by depressive symptoms group

Using the dichotomous cutoff (CES-D score ≥ 16), 36 (28.3%) survivors were classified as having depressive symptoms. The average CES-D score was 21.9 (SD = 7.3, median = 20) and 8.5 (SD = 4.1, median = 9) for survivors with and without depressive symptoms, respectively. Table 2 presents the distribution of HCC survivors by depressive symptoms group. The mean age of survivors in the depressive symptoms group was 71.1 years (SD = 7.6). The mean age of survivors in the no-depressive symptoms group was 68.2 years (SD = 8.6).

There were significant differences in KPS scores, Child–Pugh grades, cohabitation, and employment between the two depressive symptoms groups. There were no differences between the depressive symptoms groups in terms of gender, age, etiology of liver disease, education, history of HCC recurrence after initial treatment, and time since treatment.

Multivariate logistic regression models of depressive symptoms

By using multivariate logistic regression procedures, four significant determinants of depressive symptoms were identified (Table 3). Having KPS scores less than 80, having Child–Pugh grade B or C, living alone, and being unemployed were associated with an increased likelihood of depressive symptoms. Multivariate logistic regression analysis with adjustment for age [16–19], KPS [16,20,21], and time since treatment [22,23], which are considered to be important factors related to depressive symptoms, yielded same results.

Depressive symptoms and health-related quality of life

The EORTC QLQ-C30 and EORTC QLQ-HCC18 scores by depressive symptoms groups are presented in Table 4. The HRQOL scores were significantly lower among HCC survivors with depressive symptoms than among survivors with no depressive symptoms in almost all domains, and the effect size was medium or large in all domains except for sexual interest. In addition to univariate analysis, we conducted a multivariate regression analysis with adjustment for age [24–26], gender [27], KPS [28], Child–Pugh grade [27,29,30], and history of

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Table 2. Characteristics of hepatocellular carcinoma survivors by depressive symptoms group

Variables	CES-D score: Depressive symptoms ($n=36$)	CES-D score: No depressive symptoms ($n=91$)	p-value
Gender			0.05
Male	18 (50.0)	63 (69.2)	
Female	18 (50.0)	28 (30.8)	
Age (years)[a]	71.1 ± 7.6	68.2 ± 8.6	0.08
Employment status			0.001
Employed	6 (16.7)	44 (48.3)	
Unemployed	30 (83.3)	47 (51.7)	
Education			0.11
≤12 years	13 (36.1)	70 (76.9)	
>12 years	23 (63.9)	21 (23.1)	
Cohabitation status			<0.0001
Living with family or other adults	15 (41.6)	70 (76.9)	
Living alone	21 (58.4)	21 (23.1)	
Karnofsky performance status			<0.0001
80–100	26 (72.2)	87 (95.6)	
Less than 80	10 (27.8)	4 (4.4)	
Etiology of liver disease			
Hepatitis C virus			0.27
Yes	24 (66.7)	51 (56.0)	
No	12 (33.3)	40 (44.0)	
Hepatitis B virus			0.93
Yes	12 (33.3)	31 (34.1)	
No	24 (66.7)	60 (65.9)	
Comorbidity other than chronic liver disease			0.31
Yes	26 (72.2)	57 (62.6)	
No	10 (27.8)	34 (37.4)	
Child–Pugh grade			<0.0001
A	20 (55.6)	76 (83.5)	
B/C	16 (44.4)	15 (16.5)	
History of HCC recurrence after initial treatment			0.78
Yes	24 (66.7)	63 (69.2)	
No	12 (33.3)	28 (30.8)	
Time since treatment, months[a]	27.3 ± 18.7	27.6 ± 18.4	0.34

Values are expressed as numbers (%) unless otherwise specified. Higher Karnofsky performance scores signify better performance status. Liver function becomes worse with increasing Child–Pugh grades A, B, and C. CES-D, Center for Epidemiologic Studies Depressive symptoms Scale; HCC, hepatocellular carcinoma.
[a]Data are expressed as mean (standard deviation).

Table 3. Multivariate logistic regression model for depressive symptoms in hepatocellular carcinoma survivors

Variable	Adjusted OR	95% CI	p-value
KPS			
Less than 80	4.59	1.03–20.35	0.04
80–100 (ref)	1.00		
Child–Pugh grade			
B/C	3.22	1.11–10.0	0.03
A (ref)	1.00		
Cohabitation status			
Living alone	6.87	2.53–18.63	<0.001
Living with family or other adults (ref)	1.00		
Employment status			
Unemployed	5.18	1.73–15.54	0.003
Employed (ref)	1.00		

OR, odds ratio; KPS, Karnofsky performance status.

HCC recurrence after initial treatment [25,26,29], which are considered to be important factors related to HRQOL in HCC patients. As expected, depressive symptoms were independent factors related to almost all domains of HRQOL.

Discussion

To our knowledge, this is the first study that investigated the prevalence and determinants of depressive symptoms among the HCC survivors after their curative treatment. And this is the first study to investigate the impact of depressive symptoms on HRQOL precisely, using HCC-specific module. The prevalence of depressive symptoms among the HCC survivors was 28.3%. The multiple logistic regression

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DOI: 10.1002/pon

Table 4. Comparison of EORTC QLQ-C30 and EORTC QLQ-HCC18 scores between HCC survivor depressive symptoms groups

	Depressive symptoms ($n=36$)	No depressive symptoms ($n=91$)	Effect size[a]	p-value
EORTC QLQ-C30[b]				
Global health status/QOL[c]	50.9 ± 18.9	73.8 ± 17.7	1.25[d]	<0.0001
Functional scales[c]				
Physical function	72.0 ± 19.8	89.6 ± 11.6	1.08[d]	<0.0001
Role function	69.4 ± 28.3	91.0 ± 15.8	0.94[d]	<0.0001
Emotional function	71.5 ± 20.4	89.6 ± 12.0	1.08[d]	<0.0001
Cognitive function	64.8 ± 26.6	80.7 ± 17.0	0.71[d]	0.0007
Social function	75.5 ± 25.6	91.4 ± 15.8	0.75[d]	0.0002
Symptom scales[e]				
Fatigue	44.7 ± 23.1	24.3 ± 18.5	0.97[d]	<0.0001
Pain	26.8 ± 13.8	6.4 ± 29.6	0.88[d]	0.0003
Nausea/vomiting	3.7 ± 6.4	1.5 ± 8.1	0.30[f]	0.14
Dyspnea	25.9 ± 25.3	12.8 ± 19.0	0.59[d]	0.007
Appetite	25.9 ± 31.9	8.8 ± 19.1	0.65[d]	0.004
Insomnia	35.2 ± 34.7	14.3 ± 20.6	0.73[d]	0.001
Constipation	22.2 ± 20.2	12.1 ± 29.8	0.39[f]	0.06
Diarrhea	13.9 ± 23.1	6.9 ± 31.9	0.25[f]	0.10
Financial difficulties	22.2 ± 31.9	10.9 ± 31.9	0.35[f]	0.05
EORTC QLQ-HCC18[b]				
Symptom scales[e]				
Fatigue	39.5 ± 24.6	20.0 ± 18.0	0.90[d]	<0.0001
Body image	42.1 ± 28.8	22.9 ± 19.9	0.77[d]	0.0006
Jaundice	21.2 ± 16.9	10.4 ± 13.9	0.69[d]	0.006
Nutrition	22.4 ± 18.5	9.7 ± 9.8	0.86[d]	0.0004
Pain	22.2 ± 16.4	10.4 ± 13.1	0.79[d]	0.0003
Fever	9.7 ± 14.6	2.6 ± 7.8	0.60[d]	0.007
Abdominal swelling	34.3 ± 31.4	12.4 ± 18.4	0.85[d]	0.0003
Sexual interest	11.4 ± 22.8	8.4 ± 22.3	0.13[g]	0.51

Data are expressed as mean ± standard deviation.
QOL, quality of life; EORTC, European Organization for Research and Treatment of Cancer.
[a]Cohen's *d*.
[b]Scale scores range from 0 to 100.
[c]Higher score indicates higher QOL.
[d]Large effect size.
[e]Higher score indicates lower QOL.
[f]Medium effect size.
[g]Small effect size.

analysis revealed that the determinants of depressive symptoms included poor KPS, poor liver function, living alone, and unemployment. Survivors with depressive symptoms had poorer HRQOL in almost all domains compared with survivors with no depressive symptoms.

The prevalence of depressive symptoms (28.3%) among the HCC survivors was slightly higher than that reported for other liver diseases, such as chronic liver disease (23.6%) [31] and hepatitis C (20.0–28.0%) [32,33]. The patients in this study continued to suffer from hepatitis or cirrhosis even after being treated for HCC. Furthermore, specific problems, such as the burden of other symptoms, the uncertainty of treatment outcomes, the fear of recurrence, and the probable change in socioeconomic status, may contribute to depressive symptoms in cancer survivors [34]. These factors may be responsible for the observation of a higher prevalence of depressive symptoms in HCC survivors compared with that observed in chronic liver disease or hepatitis C patients.

The prevalence of depressive symptoms among the HCC survivors was higher than that reported among survivors of prostate cancer (17.0%) [35] or breast cancer (23.0%) [36] but lower than that reported among survivors of colorectal cancer (36.7%) [6]. Colorectal cancer survivors may have associated changes in bowel habit, and sexual or micturition problems after surgery, leading to a higher prevalence of depressive symptoms among them. Colorectal cancer patients undergo postoperative adjuvant therapy such as chemotherapy or radiotherapy. Although postoperative loss of function and the symptoms caused by adjuvant therapy are thought to contribute to depressive symptoms in other cancer survivors, HCC patients rarely undergo adjuvant therapy, and no functions are lost through treatment. Nevertheless, the fact that the prevalence of depressive symptoms among HCC survivors is similar to or higher than that among other cancer survivors indicates the need to take precautions against depressive symptoms in HCC patients.

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DOI: 10.1002/pon

To increase our knowledge of the factors associated with depressive symptoms among HCC survivors, we compared the depressive symptoms groups with a variety of sociodemographic and clinical variables. Our results indicate that sociodemographic and psychosocial variables such as living alone and being unemployed, in addition to physical variables such as poor KPS and decreased liver function, were associated with depressive symptoms. Previous studies with survivors of other cancers have identified physical [19,37], sociodemographic [17,38], and psychosocial variables [20,39–42] and modifiable health behaviors [43] to be important factors associated with depressive symptoms. We found these to be true for the survivors of HCC in our study and found that poor liver function was an HCC survivor-specific factor associated with depressive symptoms. HCC survivors continue to suffer from hepatitis or cirrhosis after curative treatment for HCC. With the progression of liver cirrhosis, they suffer from ascites, hepatic encephalopathy, and various physical symptoms, which may contribute to a higher psychological distress than other cancers. Healthcare professionals need to keep a close eye on the decrease of liver function after curative treatment.

Previous studies regarding the survivors of various types of cancer have indicated that depressive symptoms are associated to HRQOL [4]. In our study, we showed that depressive symptoms are strongly related to almost all domains of EORTC QLQ-C30 and HCC-specific module, EORTC QLQ-HCC18. The effect size was medium or large in all domains except for sexual interest, suggesting a big difference between individuals with depressive symptoms and those without. Thus, continuous screening for depressive symptoms of HCC survivors is warranted because it is a symptom that healthcare professionals tend to underestimate [44].

Our study was subject to some limitations. First, it was of cross-sectional design; therefore, no causal relations among the variables and depressive symptoms could be established. The study was conducted on a small number of HCC survivors at one hospital, and therefore, the findings may not be generalized to other populations. Second, we did not perform standardized psychiatric interviews; however, the CES-D has been shown to be a reliable and valid screening instrument for depressive symptoms. Third, we could not include age-matched and gender-matched noncancer control. This would be the subject for our further research. Fourth, we could not include variables such as mental disorder prior to cancer and health behavior. Future research should evaluate additional variables related to depressive symptoms following HCC treatment and their impact on HRQOL. Fifth, depressive symptoms and HRQOL based on the type of treatments received could not be explored in this study, as patients had varying treatment durations, types of treatment, and times between treatments.

Despite these limitations, this study contributes to highlight a potential target group for the intervention to prevent and treat depressive symptoms in HCC survivors.

Conclusion

This study found that many HCC survivors experienced depressive symptoms after their curative treatment. Depressive symptoms were influenced by sociodemographic and clinical factors and had a negative impact on HRQOL, with poorer scores in almost all domains among patients with depressive symptoms. Healthcare professionals should pay more attention to the possibility of depressive symptoms among HCC survivors with poor KPS, poor liver function, who live alone, and/or are unemployed. Interventions for depressive symptoms among patients with cancer have been shown to be effective; therefore, we believe that implementing a program geared toward HCC patients and survivors would be beneficial. Because multiple physical and social factors were associated with depressive symptoms among the HCC survivors, it is important to provide comprehensive interdisciplinary interventions in addition to normal treatment for depressive symptoms. Future research should evaluate additional variables related to depressive symptoms following HCC treatment and their impact on HRQOL over time.

Acknowledgements

This study was supported in part by the Third-Term Comprehensive Control Research for Cancer from the Japanese Ministry of Health, Labour and Welfare (grant no. 22092401). The authors thank all the patients who took part in this study. The authors also thank Hiroyasu Esumi for his support. The data in this paper were presented in part at the 50th Annual Meeting of Japan Society of Clinical Oncology.

Conflict of interest

The authors of this study did not receive any financial support for this study and declare no conflict of interest.

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Support Care Cancer (2013) 21:3393–3402
DOI 10.1007/s00520-013-1910-8

ORIGINAL ARTICLE

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

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Received: 16 May 2013 / Accepted: 12 July 2013 / Published online: 10 August 2013
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Abstract
Context The Japan Outreach Palliative Care Trial of Integrated Model (OPTIM) study, a mixed-methods study to evaluate the effects of a comprehensive regional palliative care program, revealed that the program provided broad positive outcomes at the regional level: increased home death, palliative care use, patient- and family-reported qualities of care, and health care professionals' difficulties. Not all participants however obtained positive outcomes and thus exploring the reasons why expected outcomes were observed in individual levels could be of value.
Aims The primary aims were to explore why expected outcomes were not obtained in individual participants, and the perceived changes in daily practices of physicians and nurses were explored.
Subjects and methods Postintervention questionnaire survey on 857 patients, 1,137 bereaved family members, 706 physicians, and 2,236 nurses were analyzed.
Results The reasons for not achieving home deaths included unexpected rapid deterioration, caregivers unavailable, concerns about adequate responses to sudden changes, and physical symptoms uncontrolled, while lack of physician availability at home and lack of information from physicians were less frequently reported. The reasons for not receiving specialized palliative care services were the lack of recommendations from physicians and no information about

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

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

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

Introduction

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

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

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

Subjects and methods

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

Overview of the OPTIM study [17]

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

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

Subjects

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

Patients

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

Bereaved families

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

Physicians and nurses

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

Measurements

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

Reasons why patients did not die at home

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

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

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

Reasons why patients did not receive palliative care services

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

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

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

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

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

Perceived changes in physicians and nurses

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

Statistical analyses

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

Results

Why patients did not die at home?

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

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

Why patients did not receive palliative care services?

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

Table 1 Reasons why patients did not die at home

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

For physicians and nurses, values are total number of responses of agree or slightly agree

CI confidence intervals

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

The main reasons for not receiving specialized palliative care services observed in patients and families were the lack of recommendations from physicians and no information about how to consult palliative care services. In addition, 40 % of the patients listed minimal interference with daily life and 25 % received an explanation that symptoms would continue only for short periods as a reason. About 60 % of the physicians reported that they encountered no patients with unpalliated symptoms, and 15 % reported that they were unaware palliative care services were available.

Table 2 Reasons why patients did not receive palliative care services

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

For physicians, values are total number of responses of agree or slightly agree

CI confidence intervals

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

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

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

Perceived changes of physicians and nurses

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

Discussion

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

Why patients did not die at home?

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

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

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

For physicians, values are total number of responses of agree or slightly agree

CI confidence intervals

Table 4 Perceived changes of physicians and nurses in daily practice

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

Values are total number of responses of agree or slightly agree

NA not available

[a] Among all professions

[b] Hospital physician (HP) vs. all other professions

[c] GP vs. all other professions

[d] Hospital nurse (HN) vs. all other professions

[e] District nurse (DN) vs. all other professions

[f] HP vs. GP

[g] HN vs. DN

[h] HP vs. HN

[i] GP vs. DN

rapid deterioration and caregivers unavailable are understandable because no intervention is specifically aimed to facilitate an education program about survival estimation for physicians and to enhance informal caregiver resources [16]. As multiple studies have demonstrated that clinicians are significantly likely to overestimate the prognosis of terminally ill patients [18] and that the presence of formal and informal caregivers is one of the most important determinants of home death [8, 9], systematic efforts to improve physician prognostication, such as the dissemination of validated prognostic tools and facilitating proactive strategies throughout the region [19–21], and reconstructing social resources to optimize formal and informal caregivers, are necessary to achieve more home death. Against uncontrolled physical symptoms as a reason for discontinuing staying at home, this study encouraged community palliative care team and a continuing effort to establish community palliative care services is highly valuable [22–24]. To lessen concerns about adequate responses to sudden changes, the health care system of 24-h 7-day service is more encouraged.

Why patients did not receive palliative care services?

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

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

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

This study revealed that about 20 % of patients and families evaluated the quality of palliative care as still requiring improvement. The major reasons were clinicians actually tried to relieve symptoms but limited effects and insufficient time; that is, negative attitudes of clinicians were rarely reported by patients and families. The majority of physicians and nurses surveyed reported that they respected patients' hopes and paid greater attention to families. A possible interpretation of this result is that physicians and nurses actually made maximum efforts to relieve patients' distress within the limited time allowed, but patient distress often demonstrated no apparent improvement due to (1) the refractory nature of the symptom (e.g., fatigue, anorexia, neuropathic or incidental pain); (2) nonreferral to palliative care services, resulting in failure to optimize symptom palliation; or 3) lack of time to address complex psychological, social, and spiritual issues, resulting in unsatisfactory outcomes. Potential systematic resolutions include (1) research to identify effective palliative treatment of difficult symptoms [28–30] and (2) ensuring enough time for each clinician to address patients' concerns.

Physician- and nurse-perceived changes during the study period

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

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