象についての質問が多くなったこと，利用者が増すにつれ有害反応に対する危惧が増していること，同時に患者からの有効性検証の要望が増していることなどが考えられる．次第に我が国でも臨床腫瘍医にとって避けて通れない問題となりつつある．最近，日本の医師の CAM に対する認識を調査した論文が，いくつかの英文誌に掲載されている[19,20]．全国 751 名の臨床腫瘍医のアンケート調査結果では，腫瘍医の 82%は CAM で使用される健康食品類にはがんに対する有効性は無いと考え，その理由として信頼できるエビデンスが無いことをあげている．また 84%の腫瘍医が抗がん剤との相互作用を危惧していると答えている．

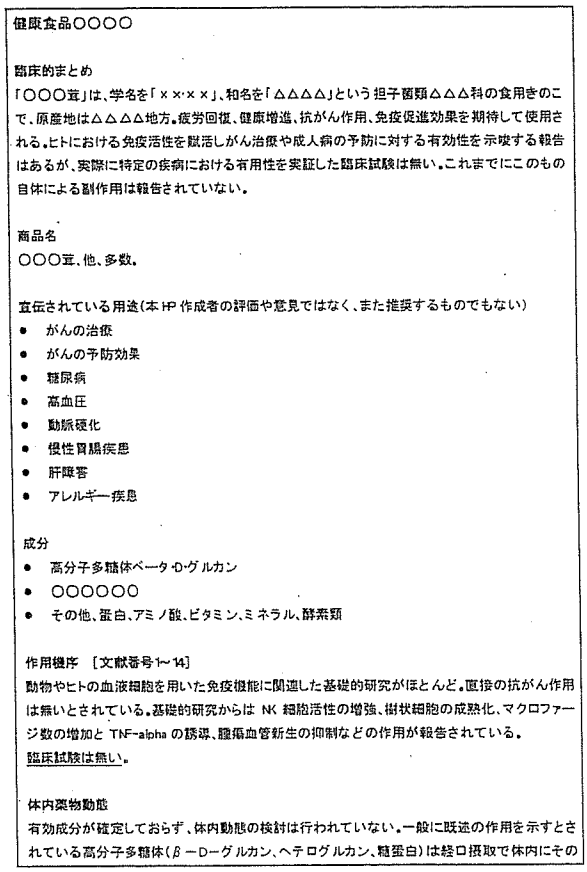
6. 健康食品の問題

がんで使用される CAM のうち健康食品の利用は最も多い．しかし，これまでに健康食品ががん患者に対していかなる効果であれ，明らかな効果をもたらしたという明快な科学的証拠はほとんど無い．現在，健康食品を定義する法律はなく，一般的に健康維持の目的で用いられ，通常の食品とは異なる形態の粒状，カプセル状などの食品と考えられている．薬理的作用により疾病の予防や改善が期待される食品（高血圧や糖尿病などに良いとされるものなど）で，法的に規定されているものには特定保健用食品がある．平成 15 年 10 月 7 日現在，396 品目が厚生労働省より認可されている．これはあくまで通常の食品のかたちをしたもので，錠剤やカプセル状の形態をしていないものとされている．健康食品と呼ばれるものの中には錠剤，カプセル，粉末状のものを業者が健康食品と勝手に名づけて市販しているものが多い．現在，このような健康食品に対しては財団法人日本健康・栄養食品協会が含有成分などの製品規格，製造と加工の基準，適切な表示と広告（食品衛生法，薬事法，栄養改善法などに適合しているか）などを審査し JHFA マークを付与している．しかし，実際にはこのマークの無い健康食品が非常に多く存在している．

サメ軟骨の抗腫瘍効果，血管新生抑制効果が報告され[21]，現在，米国では NCI をスポンサーとして NCCTG（North Central Cancer Treatment Group）を中心に，切除不能乳がんと大腸がん患者を対象としたプラセボを使用した二重盲検無作為化比較第 III 相試験が行なわれている（表 2）．エンドポイントは生存，毒性，QOL である．国の医療事情や研究体制の違いもあるが，我が国においてもがん患者に使用される頻度の高い健康食品については，きちんとした臨床試験を行う必要がある．そのステップとして健康食品は既に世間に広く使用されているものであるから，まず確実な有効例（Best case series）の収集，次に小規模な比較試験，そして最終的には充分な検出力を有する大規模比較試験が行なわれなければならない．これと同時に副作用症例の積極的な報告が為される必要がある．

健康食品の一部には健康被害を生じているものも報告されているが[22,23]，多くのものでは健康に害を及ぼすことは無いかあるいはまれとされている．しかし，薬物と併用される場合には相互作用の可能性もあり注意しておく必要がある．グレープフルーツの成分が CYP 3A3/4 を抑制し，スタチン系の薬剤や抗ヒスタミン剤内服患者に筋肉痛や不整脈を生じることは良く知られている．現在までに抗がん剤との明らかな相互作用を有する健康食品は報告されていないが，サリチル化ハーブ類などでは理論的にはメソトレキセートや類似薬の尿への排泄を阻害する可能性がある．また前立腺がんに効果があるとされるハーブの合剤にエストロゲン作用を有する成分が含まれていたという報告もある[24]．

わが国の CAM に関する情報は，健康食品に関するものに偏っており，その圧倒的多数が「驚異の治癒力」とか「末期がんからの生還」，「○○学会で絶賛」「フェーズ III で実証」といった文言をちりばめた単行本やインターネット上のホームページによる．しかし，このようなあたかも多くの医師が認めているかのような語調の見出しでも，当該学会の実際の学会抄録には発表された形跡がなかったり，臨床試験に関する専門用語を使っただけで実体のないものが多い．かろうじて論文の体裁をとっているものでも，その多くが試験管レベルの基礎研究か一例報告であり，その効果を検証するための前向きな臨床試験あるいはメタアナリシスの結果は皆無に近いのが現状である．医薬品にしか許可されていない効能の表示は違法であり薬事法，食品衛生法，景品表示法，栄養改善法などにより規制されている．しかし，がんの予防や治療に有効性を謳う健康食品は多数存在している．医療者にとってハーブ（薬草・生薬）やキノコ類，その他の自然界の生物から得られる成分を含む健康食品に関する適切な情報の提供は緊急の課題である．最近，Memorial Sloan-Kettering Cancer Center（NY）内に設置されている Integrative Medicine Service が作成・運営しているウェブサイト（http://www.mskcc.org/mskcc/html/11570.cfm）に 135 種類のハーブや植物性薬品について，治療に用いる際の条件や有害作用，薬物相互作用などの情報を掲載している．このサイトではサプリメントに関して文献に基づき科学的検証を行った上で，その臨床的効果について客観的に記載した情報を発信している．厚生労働省の研究班においても医学的，客観的な立場から，現在我が国



健康食品○○○○

臨床的まとめ
「○○○茸」は、学名を「××××」、和名を「△△△△」という担子菌類△△△科の食用きのこで、原産地は△△△△地方。疲労回復、健康増進、抗がん作用、免疫促進効果を期待して使用される。ヒトにおける免疫活性を賦活しがん治療や成人病の予防に対する有効性を示唆する報告はあるが、実際に特定の疾病における有用性を実証した臨床試験は無い。これまでにこのもの自体による副作用は報告されていない。

商品名
○○○茸、他、多数。

宣伝されている用途(本HP作成者の評価や意見ではなく、また推奨するものでもない)
- がんの治療
- がんの予防効果
- 糖尿病
- 高血圧
- 動脈硬化
- 慢性胃腸疾患
- 肝臓病
- アレルギー疾患

成分
- 高分子多糖体ベータ-D-グルカン
- ○○○○○○
- その他、蛋白、アミノ酸、ビタミン、ミネラル、酵素類

作用機序 [文献番号1~14]
動物やヒトの血液細胞を用いた免疫機能に関連した基礎的研究がほとんど。直接の抗がん作用は無いとされている。基礎的研究からは NK 細胞活性の増強、樹状細胞の成熟化、マクロファージ数の増加と TNF-alpha の誘導、腫瘍血管新生の抑制などの作用が報告されている。
臨床試験は無い。

体内薬物動態
有効成分が確定しておらず、体内動態の検討は行われていない。一般に既述の作用を示すとされている高分子多糖体(β-D-グルカン、ヘテログルカン、糖蛋白)は経口摂取で体内にその

図2 がん患者に利用されている健康食品のまとめの一例

でがん患者に利用されている健康食品に関するサマリーを作成し，公表する予定である．その一例を図2に示した．

7. 今後の課題

世界規模で西洋医学的手法を用いたCAMに対する研究が進められている．我が国では早急にevidenceに基づくCAMのデータベースの作成，学会や公的機関による臨床試験体制の確立が望まれる．その他，CAM奏効例の収集，検証システムの開発，副作用例の集積と使用者や医療機関への周知方法，健康食品の利用方法や安全性に関するガイドラインの作成なども必要とされている．

最後にCAMに関して将来的なあり方という観点からすると，医学はひとつであり主流／非主流あるいは通常／代替などと相対すべきものではないはずである．同一の患者に二つの医学あるいは医療が存在することはありえない．これはある意味で患者にとって不幸であり，それを許容することは医学の怠慢とも考えられる．よく計画された臨床試験から得られる充分な証拠に基づいた医療こそ真の医療であり，多くの不確かなことが補完代替の名のもとに漫然と継続されることなく，順次，有効／無効，有害／無害が明らかにされていくべきであろう．

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ABSTRACT

Complementary and Alternative Medicine in Cancer Treatment

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Interest in complementary and alternative medicine (CAM) has grown rapidly, fueled by Internet marketing, dissatisfaction with mainstream medicine, and the desire of patients to be actively involved in their own health care. CAM products in cancer medicine (herbs and other natural products, such as shark cartilage, mushrooms, and so on) are widely available in Japan as well as in western countries. With little reliable information and few clinical trials to assess the efficacy of such products, there is a great need for public and professional education regarding this subject.

Key words: complementary medicine, alternative medicine, cancer treatment, clinical trial

別紙1

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患者の視点を重視したネットワークによる在宅がん患者支援システムの開発に関する研究

平成16年度～18年度　総合研究報告書

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別紙４

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Association between hydration volume and symptoms in terminally ill cancer patients with abdominal malignancies

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Background: To explore the association between hydration volume and symptoms during the last 3 weeks of life in terminally ill cancer patients.

Patients and methods: This was a multicenter, prospective, observational study of 226 consecutive terminally ill patients with abdominal malignancies. Primary responsible physicians and nurses evaluated the severity of membranous dehydration (dehydration score calculated from three physical findings), peripheral edema (edema score calculated from seven physical findings), ascites and pleural effusion (rated as physically undetectable to symptomatic), bronchial secretion, hyperactive delirium (Memorial Delirium Assessment Scale), communication capacity (Communication Capacity Scale), agitation (Agitation Distress Scale), myoclonus and bedsores.

Results: Patients were classified into two groups: the hydration group ($n=59$) who received 1 l or more of artificial hydration per day, 1 and 3 weeks before death, and the non-hydration group ($n=167$). The percentage of patients with deterioration in dehydration score in the final 3 weeks was significantly higher in the non-hydration group than the hydration group (35% versus 14%; $P=0.002$), while the percentages of patients whose symptom scores for edema, ascites and pleural effusion increased were significantly higher in the hydration group than the non-hydration group (44% versus 29%, $P=0.039$; 29% versus 8.4%, $P<0.001$; 15% versus 5.4%, $P=0.016$; respectively). After controlling for multiple covariates and treatment settings, the association between hydration group and dehydration/ascites score was statistically significant. Subgroup analysis of patients with peritoneal metastases identified statistically significant interaction between hydration group and dehydration/pleural effusion score. There were no significant differences in the degree of bronchial secretion, hyperactive delirium, communication capacity, agitation, myoclonus or bedsores.

Conclusions: Artificial hydration therapy could alleviate membranous dehydration signs, but could worsen peripheral edema, ascites and pleural effusions. It is suggested that the potential benefits of artificial hydration therapy should be balanced with the risk of worsening fluid retention symptoms. Further clinical studies are strongly needed to identify the effects of artificial hydration therapy on overall patient well-being, and an individualized treatment and close monitoring of dehydration and fluid retention symptoms is strongly recommended.

Key words: dehydration, neoplasm, palliative care, rehydration, water depletion

Introduction

The dehydration–rehydration problem has been one of the most important issues in palliative or end-of-life care literature over the two last decades [1]. Current discrepancies in the practice of artificial hydration therapy for terminally ill cancer patients have the potential to cause serious clinical problems: patients could suffer from unnecessary dehydration-related

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symptoms or experience iatrogenic over-hydration symptoms [2–5]. These discrepancies are largely due to the lack of evidence about the effects of artificial hydration therapy on patient well-being [3].

Traditionally, artificial hydration therapy has been thought not to benefit the terminally ill [6–11]; however, some recent studies have demonstrated that appropriate hydration can contribute to patient comfort [12–16]. The majority of studies on this topic are limited by methodological issues [17], and do not provide enough of a basis for the evidence-based practice of artificial hydration therapy in terminally ill patients. The aim of the present study was to explore systematically the associations between hydration volume and dehydration and fluid retention symptoms in the last 3 weeks of life in terminally ill patients with abdominal malignancies.

Patients and methods

Patients

The study subjects were consecutive terminally ill cancer patients treated in 14 oncology units, 19 palliative care units and four home-based palliative care programs in Japan. The participating institutions recruited potential participants following the same inclusion criteria: age >20 years; life expectancy estimated by a physician to be ≤3 months; and incurable malignancy of abdominal origin (excluding hepatic malignancies). Exclusion criteria were: liver cirrhosis of any etiology, renal failure, nephrotic syndrome, protein-losing enteropathy, intra-abdominal shunt for ascites, hypercalcemia, adrenalopathy, thyroid diseases, and other complications of the circulatory, respiratory, hepatic, or renal system unrelated to underlying malignancies; surgical, radiological or oncological treatments with the primary intent of tumor reduction in the 3 weeks prior to study inclusion; existing communication difficulty such as aphasia or aphonia; and the use of artificial enteral nutrition. Patients were enrolled from August 2002 to February 2003, and followed until March 2003.

Study design

This was a multicenter, prospective, observational study. From the time of study inclusion, primary responsible physicians prospectively recorded patients' dehydration and fluid retention symptoms on a structured data-collecting sheet every week as a part of daily practice. In addition, symptoms observed very close to death were assessed after patients died, because it was impossible to predict when the patients would die, and because assessments on a daily basis would present a high burden for patients and physicians. Thus, within 72 h after patient death, patients' dehydration and fluid retention symptoms 24 h before death, communication capacity during the 3 days before death and degree of agitation in the week before death were recorded. To minimize the recall bias, the evaluations were based on the full agreement of the primary physicians and primary nurses.

The patients received the usual treatments from their institutions. The indications for hydration therapy, administration methods and modification of treatment regimen over time were dependent on each physician's clinical decisions. We did not standardize hydration treatments, because patients' and families' wishes and each physician's philosophy strongly influenced actual hydration practice [3], and adopting a single hydration protocol was regarded as inappropriate outside experimental study designs. Instead, we described the details of hydration treatments actually performed for interpretation of the results.

This study was approved by the Institutional Review Board of each hospital, and conducted in accordance with the Declaration of Helsinki.

End points and measurements

The primary end points of this study were dehydration and fluid retention symptoms in the last 3 weeks of life. Although patient-reported symptoms and satisfaction are important outcomes in palliative care [18], we chose symptoms that could be objectively evaluated as the end points for this study. The rationale for this decision was that adopting self-report measures could result in higher rates of patient exclusion and unacceptable selection bias, because patient reports are often impossible in the very late stages of cancer due to cognitive impairment, and because symptom evaluations based on patient self-reports are not routinely used in many participating institutions [19, 20].

Physical symptoms

Physicians were requested to perform physical examinations in the morning at least 1 h after patients had eaten. The degree of dehydration was assessed on the basis of three physical findings: moisture on the mucous membranes of the mouth (0, moist; 1, somewhat dry; 2, dry), axillary moisture (0, moist; 1, dry) and sunkenness of eyes (0, normal; 1, slightly sunken; 2, sunken). These signs were selected due to their significant correlations with biological dehydration, as previously confirmed in elderly patients [21–23]. Empirical studies have found that the sensitivity/specificity of each sign in identifying dehydration is 85%/58%, 50%/82% and 62%/82%, respectively [21–23]. *Ad hoc* dehydration score (range 0–5) was calculated as the total of these three scores. A higher score thus indicated a higher level of dehydration.

The severity of peripheral edema was determined through the examination of seven regions: the hands, forearms, upper arms, feet, lower legs, thighs and trunk. Peripheral edema severity was scored based on the degree of increased skin thickness in the middle of each region (0, none; 1, mild, thickness of <5 mm; 2, moderate, 5–10 mm; 3, severe, >10 mm). If peripheral edema was asymmetric, the more severe side was rated unless the asymmetry was caused by a unilateral vascular obstruction; in these cases, the non-obstructed side was rated. The peripheral edema score (range 0–21) was calculated as the total of the severity scores for the seven regions. A higher score indicated more severe edema.

Pleural effusion and ascites were each rated on a scale of 0 to 2 (0, physically non-detectable; 1, physically detectable but asymptomatic; 2, symptomatic or tense ascites). Myoclonus and bedsores were considered present when they were observed at any time in the final 3 weeks of life.

Bronchial secretion was defined as sounds audible at the bedside produced by movement of secretions in the hypopharynx or the bronchial tree in association with respiration [8]. The severity of bronchial secretion was evaluated using a previously proposed scale: 'inaudible' (score 0), 'audible only very close to the patient' (score 1), 'clearly audible at the end of the bed in a quiet room' (score 2) and 'clearly audible at about 6 m or at the door of the room' (score 3) [24]. Bronchial secretions were considered present when patients had a severity score of 1 or more, received any anti-muscarinic medications to reduce bronchial secretion or received oral/bronchial suctioning at least once during the final 3 weeks of life. Severe bronchial secretion was defined as severity score of 2 or 3 at any time during the final 3 weeks.

Psychiatric symptoms

We used selected items of the Communication Capacity Scale, the Agitation Distress Scale and the Memorial Delirium Assessment Scale to evaluate psychiatric symptoms [25, 26]. The Communication Capacity Scale is a validated five-item observer-rating scale used to quantify communication

capacity in terminally ill patients [25]. The Agitation Distress Scale is a six-item observer-rating scale used to quantify the levels of agitation in delirious terminal patients [25]. Although using all items of a scale is psychometrically ideal, we used select items in order to reduce physician burden and increase patient enrollment [27].

The patients' communication capacity was assessed using the highest scores measured in the last 3 days of life on three items: the 'reduced level of consciousness' item of the Memorial Delirium Assessment Scale, and the 'answers to closed-ended questions' and 'voluntary communication' items from the Communication Capacity Scale. Communication score (range 0–9) was calculated as the total of these three items, such that a higher score indicated a greater capacity for communication (Cronbach's α coefficient = 0.94). The correlations between total score on this abbreviated scale and the total score on the Communication Capacity Scale was high in the original validation data (Spearman's $\rho = 0.94$; $P < 0.001$) [25].

The degree of agitation was defined as the most severe symptoms experienced during the last week of life, and quantified using four items from the Agitation Distress Scale: the frequency of motor anxiety, extent of motor anxiety, contents of motor anxiety and psychological instability. The agitation score (range 0–12) was calculated as the total of these four items; a higher score indicated higher levels of agitation (Cronbach's α coefficient = 0.87). The correlations between total score on this abbreviated scale and the total score on the Agitation Distress Scale was high in the original validation data (Spearman's $\rho = 0.95$; $P < 0.001$) [25].

Hyperactive delirium was assessed using the 'psychomotor activity' item of the Memorial Delirium Assessment Scale, which grades increased psychomotor activity on a scale of 0 (normal) to 3 (severe) [26]. Hyperactive delirium was defined as a score of 2 or 3 on this scale.

Covariates of main outcomes

We recorded the presence or absence of the following potential covariates: stomatitis, oxygen requirement, and use of opioids, diuretics and anticholinergic medication (dehydration score); vascular obstruction, and use of non-steroidal anti-inflammatory drugs (NSAIDs), steroids and diuretics (edema score); peritoneal and liver metastasis (ascites); lung and pleural metastasis, and pneumonia (pleural effusion); and intestinal obstruction and oral intake of fluids (for all symptoms) [6, 8, 15, 28].

Statistical analyses

We analyzed data for patients who died at least 3 weeks after their initial evaluation. The rationale for this decision was that we had no appropriate instruments to indicate reliable base-line points for analyses, and hydration therapy was likely to influence patient symptoms after a considerable time lag (i.e. hydration volume the patients had received 1–3 weeks before death could affect patients symptoms 48 h before death). To examine a bias, we compared patient backgrounds between the excluded and included patients.

We divided patients into two groups: those who received artificial hydration of 1 l/day or more both 1 week and 3 weeks before death (hydration group: total $n = 59$; 31 from oncology and 28 from palliative/home-care settings) and those who did not (non-hydration group: total $n = 167$ [18], from oncology and 149 from palliative/home-care settings). This classification was determined on the basis of actual data distributions, and the results using the other classifications achieved the similar conclusions.

To explore the potential association between hydration groups and patient symptoms, we compared the number of patients whose symptom scores increased in the final 3 weeks (dehydration and edema scores by three or more points; ascites and pleural effusion scores by one or more point) between the hydration and non-hydration groups. The results using the other cut-off points achieved the same conclusions. We also compared the prevalence of bronchial secretion, hyperactive delirium, myoclonus and bedsores, the degree of communication capacity, and the degree of agitation between the two groups.

To explore the effects of covariate factors and treatment settings, we examined the potential interactions between hydration groups and changes in dehydration score, edema score, and ascites and pleural effusion severity scores by the repeated measurement analysis with the covariates entered into the models (robust variance with the Proc mixed procedure). No covariates except for peritoneal metastasis and treatment settings statistically influenced the outcomes. In addition, subgroup analyses for patients who drank <500 ml/day of fluids throughout the last 3 weeks of life ($n = 108$), patients with intestinal obstruction ($n = 114$) and patients who received no intestinal drainage ($n = 192$) achieved the same results. We therefore reported the results for the entire sample with adjusted P values to allow for difference in peritoneal metastasis and treatment settings, as well as subgroup analysis of patients with peritoneal metastases ($n = 145$).

Finally, to provide additional information for interpreting data, we compared the changes in blood urea nitrogen/creatinine levels between hydration and non-hydration groups using repeated measurement analysis. We also calculated the prevalence of fluid retention symptoms 24 h before death among dehydrated patients, defined as presence of dry axillary (diagnosis on the basis of sunken eyes achieved similar results).

Univariate analyses were conducted using the χ^2-test (Fisher's exact method) and the Mann–Whitney U-test, where appropriate. All analyses were performed using the statistical package SAS.

Results

Patient background

All 498 patients who met the inclusion criteria were consecutively recruited for this study, but a total of 272 patients were excluded for the following reasons: death within 3 weeks of initial assessment ($n = 200$), survival beyond the observation period ($n = 35$), medical complications ($n = 17$), prior communication difficulty ($n = 15$) and discharge ($n = 5$). Thus, a total of 226 patients (49 from oncology units and 177 from palliative/home-care settings) were finally analyzed. There were no statistically significant differences in patient age and primary tumor sites between the patients excluded from the study due to death within 3 weeks and those analyzed, but the former was more likely to be male (Table 1).

Patient backgrounds are summarized in Table 2. There were significant differences in primary tumor sites, prevalence of lung and peritoneal metastases, vascular obstruction, intestinal obstruction, the use of NSAIDs and steroids, and oral intake 3 weeks and 1 week before death between the hydration and non-hydration groups. Chemotherapy was performed in seven patients.

Table 3 summarizes hydration practice in the study subjects. The mean hydration volume in the hydration group ranged from 838 to 1405 ml/day during the last 3 weeks, and the median hydration volume in the non-hydration group was 200 ml/day at all three observation points.

At baseline, ascites was present but asymptomatic in 27% ($n = 62$) and symptomatic in 20% ($n = 44$) of all patients.

Table 1. Characteristics of excluded and included patients

	Excluded patients[a] ($n=200$)	Included patients ($n=226$)	P
Age, years (mean ± SD)	67 ± 12	68 ± 12	0.63
Gender			
Male	114	106	0.037
Female	86	120	
Primary site			
Stomach	76	74	0.25
Colon	35	47	
Pancreas	36	35	
Rectum	15	31	
Bile duct	15	12	
Ovary	5	10	
Others	18	17	

[a]Patients who died within 3 weeks of initial assessment.
SD, standard deviation.

Pleural effusion was present but asymptomatic in 12% ($n=27$) and symptomatic in 6.6% ($n=15$) of all patients.

Dehydration

The percentage of patients whose dehydration score increased by three or more points in the final 3 weeks of life was significantly higher in the non-hydration group than in the hydration group [35% ($n=59$) versus 14% ($n=8$); $P=0.0020$]. After controlling for covariates and treatment settings, there was a statistically significant interaction between hydration group and changes in the dehydration score (1.6 ± 1.4 3 weeks before death to 2.7 ± 1.6 24 h before death in the hydration group versus 1.3 ± 1.3 to 3.2 ± 1.5 in the non-hydration group; $P=0.0043$) (Figure 1).

Edema

The number of patients whose edema scores increased by three or more points was significantly higher in the hydration group than in the non-hydration group [44% ($n=26$) versus 29% ($n=49$); $P=0.039$]. After controlling for covariates and treatment settings, the interaction between hydration group and changes in the edema score did not reach statistical significance (2.2 ± 3.3 3 weeks before death to 6.1 ± 6.4 24 h before death in the hydration group versus 3.5 ± 4.5 to 5.2 ± 5.2 in the non-hydration group; $P=0.15$) (Figure 1).

Ascites

The percentage of patients whose symptom score increased by one or more point during the final 3 weeks was significantly higher in the hydration group than in the non-hydration group [29% ($n=17$) versus 8.4% ($n=14$); $P<0.001$]. After controlling for covariates and treatment settings, there was a statistically significant interaction between hydration group and changes in the ascites score (0.73 ± 0.78 3 weeks before death to 0.92 ± 0.88 24 h before death in the hydration group versus 0.64 ± 0.79 to 0.58 ± 0.74 in the non-hydration group; $P=0.035$) (Figure 1).

Table 2. Patient characteristics

Characteristic	Hydration group ($n=59$) [% (n)]	Non-hydration group ($n=167$) [% (n)]	P
Age, years (mean ± SD)	67 ± 13	68 ± 11	0.36
Gender			
Male	58 (34)	43 (72)	0.055
Female	42 (25)	57 (95)	
Primary site			
Stomach	49 (29)	27 (45)	0.008
Colon	20 (12)	21 (35)	
Pancreas	19 (11)	14 (24)	
Rectum	5.1 (3)	17 (28)	
Bile duct	3.4 (2)	6.0 (10)	
Ovary	0	6.0 (10)	
Others	3.4 (2)	9.0 (15)	
Metastatic sites			
Lung	12 (7)	30 (50)	0.006
Pleura	15 (9)	15 (25)	0.96
Liver	46 (27)	44 (73)	0.79
Peritoneum	78 (46)	59 (99)	0.010
Performance status at enrolment			
≥2	29 (17)	19 (31)	0.59
3	37 (22)	42 (70)	
4	34 (20)	40 (66)	
Medical complications			
Stomatitis	12 (7)	23 (39)	0.060
Vascular obstruction of both extremities	1.7 (1)	12 (20)	0.018
Intestinal obstruction	64 (38)	46 (76)	0.013
Pneumonia	15 (9)	16 (27)	0.87
Medical treatments			
Oxygen	69 (41)	55 (92)	0.053
NSAIDs	53 (31)	71 (119)	0.009
Opioids	81 (48)	84 (141)	0.58
Steroids	54 (32)	75 (126)	0.002
Diuretics	34 (20)	32 (53)	0.76
Anti-cholinergic medications	20 (12)	25 (42)	0.46
Oral intake fluids ≥500 ml/day			
3 weeks before death	80 (47)	42 (70)	<0.001
1 week before death	83 (49)	57 (96)	<0.001
24 h before death	86 (51)	84 (140)	0.63

SD, standard deviation; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 3. Hydration practice in the final 3 weeks

	3 weeks before death [% (*n*)]	1 week before death [% (*n*)]	24 h before death [% (*n*)]
All patients			
<500 ml/day	44 (100)	48 (109)	62 (139)
500–1000 ml/day	21 (47)	22 (49)	21 (48)
≥1000 ml/day	35 (79)	30 (68)	17 (39)
Hydration group ($n=59$)			
Hydration volume, ml/day [mean ± SD (median)]	1405±479 (1300)	1253±379 (1100)	838±580 (1000)
Continuous administration	63 (37)	66 (39)	61 (36)
Intermittent administration	37 (22)	34 (20)	24 (14)
Via a central vein	76 (45)	75 (44)	61 (36)
Via a peripheral vein	24 (14)	25 (15)	22 (13)
Hyperalimentation	56 (33)	54 (32)	31 (18)

SD, standard deviation.

Pleural effusion and bronchial secretion

The number of the patients whose pleural effusion symptom score increased by one or more point in the final 3 weeks was significantly higher in the hydration group than in the non-hydration group [15% ($n=9$) versus 5.4% ($n=9$); $P=0.016$]. Hydration group was not significantly associated with changes in the pleural effusion symptom score after controlling for covariates and treatment settings (0.22±0.46 3 weeks before death to 0.36±0.61 24 h before death in the hydration group versus 0.27±0.60 to 0.31±0.63 in the non-hydration group; $P=0.76$) (Figure 1).

There was no statistically significant difference in the prevalence of bronchial secretion between the hydration and the non-hydration groups (Table 4).

Communication capacity, agitation and delirium

There were no statistically significant differences in the communication score, agitation score or prevalence of hyperactive

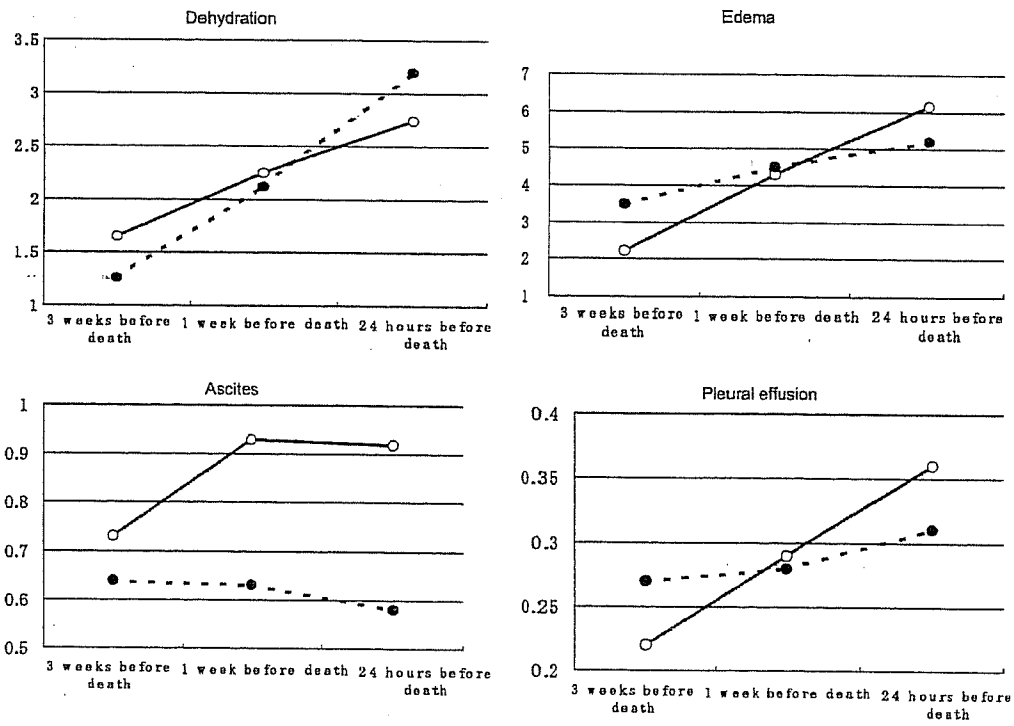

Figure 1. Effects of hydration on dehydration and fluid retention symptoms. Open circles, hydration group ($n=59$); filled circles, non-hydration group ($n=167$).

Table 4. Symptom severity in the last 3 weeks of the patients with and without hydration

	Hydration group ($n=59$)	Non-hydration group ($n=167$)	P
Bronchial secretion[a] [% (n)]	44 (26)	46 (77)	0.79
Severe bronchial secretion[b] [% (n)]	19 (11)	17 (28)	0.74
Communication score[c] (mean ± SD)	3.2 ± 3.0	3.7 ± 3.1	0.30
Agitation score[d] (mean ± SD)	2.1 ± 2.8	2.3 ± 2.7	0.35
Hyperactive delirium[e] [% (n)]	12 (7)	13 (22)	0.80

[a]Defined as audible bronchial secretion, requirement of any anti-muscarinic medications or oral/bronchial suctioning.
[b]Defined as clearly audible bronchial secretion.
[c]The total score of one item from the Memorial Delirium Assessment Scale and two items from the Communication Capacity Scale. Higher scores indicate higher levels of communication capacity.
[d]The total score of four items from the Agitation Distress Scale. Higher scores indicate higher levels of agitation.
[e]Defined as scores of 2 or 3 on the psychomotor activity item of the Memorial Delirium Assessment Scale.

delirium between the hydration and the non-hydration groups (Table 4).

Myoclonus and bedsores

There were no statistically significant differences in the prevalences of myoclonus or bedsores between the hydration and the non-hydration groups [for myoclonus 1.7% ($n=1$) versus 8.4% ($n=14$), $P=0.12$; for bedsores 27% ($n=16$) versus 34% ($n=57$), $P=0.32$].

Patients with peritoneal metastases

The interactions between hydration group and symptom changes in the last 3 weeks were statistically significant in dehydration score (1.7 ± 1.43 weeks before death to 2.9 ± 1.6 24 h before death in the hydration group versus 1.3 ± 1.3 to 3.5 ± 1.4 in the non-hydration group; $P=0.0043$) and pleural effusion score (0.22 ± 0.47 to 0.35 ± 0.60 versus 0.30 ± 0.63 to 0.27 ± 0.57, respectively; $P=0.046$), and marginally significant in ascites score (0.91 ± 0.78 to 1.0 ± 0.87 versus 0.88 ± 0.80 to 0.70 ± 0.75, respectively; $P=0.091$).

Table 5. Fluid retention symptoms in dehydrated patients ($n=149$)

	% (n)
Peripheral edema	
Hands and/or feet	69 (102)
Forearms and/or lower legs	56 (83)
Upper arms and/or thigh	36 (54)
Trunk	26 (39)
Any peripheral edema	73 (108)
Ascites	46 (69)
Pleural effusion	19 (29)
Any fluid retention symptoms	81 (121)

Dehydration was diagnosed as present if the axillary moisture was rated as dry 24 h before death.

Laboratory findings

We obtained paired blood samples taken 3 weeks and 1 week before death from 37 (63%) and 56 (34%) patients in the hydration and non-hydration groups, respectively. The blood urea nitrogen/creatinine levels increased from 34 ± 15 to 44 ± 18 mg/dl in the hydration group in the last 3 weeks, compared with from 31 ± 17 to 39 ± 20 mg/dl in the non-hydration group. The difference between hydration groups was not statistically significant ($P=0.58$).

Comorbidity of dehydration and fluid retention symptoms

Of the 149 dehydrated patients with dry axillary 24 h before death, 73%, 46% and 19% had simultaneous edema, ascites or pleural effusion, respectively; and 81% had some fluid retention symptoms (Table 5).

Discussion

This is, to the best of our knowledge, the largest and the first multicenter observation study to investigate the association between hydration volume and dehydration and fluid retention symptoms in terminally ill cancer patients.

This study revealed that peripheral edema, ascites and pleural effusion in the hydration group were more likely to worsen in the last 3 weeks. The association between hydration group and ascites severity was statistically significant after controlling all covariates and treatment settings, and in a subgroup of patients with peritoneal metastases there was a statistically significant interaction between hydration practice and changes in pleural effusion severity. The underlying mechanisms of fluid retention symptoms include a decrease in colloid osmotic pressure, an increase in membrane permeability, and an increase in hydrostatic pressure [11]. Our findings suggest that overhydration in the terminal phase could deteriorate fluid retention symptoms.

We also found that dehydration scores increased in the last 3 weeks of life regardless of whether patients received artificial hydration or not, although scores increased less in the hydration than in the non-hydration group. The potential interpretations of this finding are that: (i) the instruments for measurement of dehydration used in this study could not differentiate dehydration signs from changes related to progressed cachexia; (ii) current hydration volume was not sufficient to maintain hydration status and more active hydration could alleviate membrane dehydration signs; or (iii) artificial hydration therapy in the terminal stage could not effectively alleviate dehydration even if an appropriate volume was provided due to some pathological mechanisms (e.g. fluid shift from the intravascular components to the third space). The first