Predictive Factors for the Development of Dyspnea Within 7 Days After Admission Among Terminally Ill Cancer Patients

Matsunuma, Ryou ; Yamaguchi, Takashi ; Mori, Masanori ; Ikari, Tomoo ; Suzuki, Kozue ; Matsuda, Yoshinobu ; Matsumoto, Yoshihisa ; Watanabe,…

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Abstract

Background: Predictive factors for the development of dyspnea have not been reported among terminally ill cancer patients.

Objective: This current study aimed to identify the predictive factors attributed to the development of dyspnea within 7 days after admission among patients with cancer.

Methods: This was a secondary analysis of a multicenter prospective observational study on the dying process among patients admitted in inpatient hospices/palliative care units. Patients were divided into two groups: those who developed dyspnea (development group) and those who did not (non-development group). To determine independent predictive factors, univariate and multivariate analyses using the logistic regression model were performed.

Results: From January 2017 to December 2017, 1159 patients were included in this analysis. Univariate analysis showed that male participants, those with primary lung cancer, ascites, and Karnofsky Performance Status score (KPS) of ≤40, smokers, and benzodiazepine users were significantly higher in the development group. Multivariate analysis revealed that primary lung cancer (odds ratio [OR]: 2.80, 95% confidence interval [95% CI]: 1.47–5.31; p = 0.002), KPS score (≤40) (OR: 1.84, 95% CI: 1.02–3.31; p = 0.044), and presence of ascites (OR: 2.34, 95% CI: 1.36–4.02; p = 0.002) were

independent predictive factors for the development of dyspnea.

Conclusions: Lung cancer, poor performance status, and ascites may be predictive factors for the development of dyspnea among terminally ill cancer patients. However, further studies should be performed to validate these findings.

Keywords: dyspnea, end-of-life, predictors, development, cancer, ascites

Introduction

Dyspnea has been defined as the subjective feeling of breathing discomfort [1]. It is a distressing symptom among terminally ill cancer patients and is negatively associated with various symptoms [1]. Further, dyspnea with increasing intensity has been determined to be correlated with pain intensity, anxiety, and depression [2, 3]. Moreover, it impairs the quality of life of cancer patients and causes distress among caregivers [4]. Therefore, clinicians should consider the management of dyspnea in these patients and provide adequate and timely care to patients' caregivers [5]. Approximately 90 % of terminally ill cancer patients present with dyspnea [6, 7]. Several studies have shown that the intensity of dyspnea increases within the last 1–3 weeks of life [7, 8].

Several factors including primary and metastatic lung cancers [6, 9-11], chronic respiratory diseases (i.e., chronic obstructive pulmonary disease, asthma, asbestos-related lung disease) [9, 10, 12-15], anxiety [2], high Charlson Comorbidity Index score [16], old age [17], female sex, body mass index (>30 kg/m^2) [18], increased pleural effusion volume within several days, pneumonia, and large volume of ascites [19] have been associated with dyspnea intensity. However, to the best of our knowledge, no studies examining the predictors for the development of dyspnea among terminally ill cancer

patients have been published. There are two advantages to being able to predict the development of dyspnea at the end-of-life. First, for example, if patients require opioids for pain management, we can choose morphine with more confidence, which demonstrates the highest degree of evidence of effectiveness for dyspnea, provided the patients do not suffer from severe renal dysfunction. Second, dyspnea is one of the major conditions that can cause distress for terminally ill cancer patients and may require sedation for symptom relief. If the development of dyspnea can be predicted, it is possible to discuss end-of-life care with the patient in advance, including the desire to use sedation therapy, in preparation for the development of dyspnea that is difficult to relieve. This current study aimed to identify predictive factors for the development of dyspnea among terminally ill cancer patients admitted in inpatient hospices/palliative care units (PCUs).

Methods

Study design and participants

This was a secondary analysis of the East-Asian Collaborative Cross-cultural Study to Elucidate the Dying process (EASED), which is a multicenter prospective observational study on the dying process and end-of-life care among terminally ill cancer patients admitted to inpatient hospices/PCUs in Japan, Taiwan, and Korea. This

study has utilized the data of patients admitted to 23 inpatient hospices/PCUs in Japan. Consecutive eligible patients were enrolled in the original study if they had been recently admitted to the participating inpatient hospices/PCUs during the study period. All interventions and assessments were conducted within routine clinical practice. The inclusion criteria of this study were as follows: 1) patients aged ≥18 years, 2) those diagnosed with locally extensive or metastatic cancer (including hematological neoplasms), and 3) those who did not present with dyspnea during the initial evaluation. Meanwhile, patients who had dyspnea upon admission were excluded.

Measurement

All data were prospectively recorded by primary responsible physicians on a structured data collecting sheet designed and piloted prior to study initiation as a part of routine practice. These data were recorded starting from admission to inpatient hospices/PCUs (baseline) till death or discharge. Patient characteristics, clinical symptoms, vital signs, laboratory findings, pleural effusion and ascites, and concurrent treatment were evaluated at initial assessment. If the patients did not die within 7 days, clinical symptoms (dyspnea, insomnia, fatigue, drowsiness, and dry mouth), ascites, and infused fluid volume were assessed at 7 days after admission. If the patients were

administered opioids for relieving dyspnea, intensity of dyspnea; pleural effusion and ascites; and opioid type, dosage, and route of administration were assessed. Although these assessments were not employed in this study, opioid administration for dyspnea was used as a definition for the development of dyspnea (see details below). Moreover, if patients died within 7 days after admission, clinical symptoms including dyspnea were assessed within 3 days before death.

Characteristics of patients

Information on age, gender, height, weight, primary and metastatic lesions, comorbidities, smoking status, and performance status (PS) (assessed using the Eastern Cooperative Oncology Group and Karnofsky Performance Status [KPS]) was evaluated. Smoking status was categorized into four: none, past, current, or unknown.

Assessment of dyspnea

Dyspnea was classified into three grades: no dyspnea, dyspnea only during exertion, and dyspnea at rest [20]. Seven days after admission, physicians evaluated living patients with dyspnea using the three grades described above. When patients died, physicians assessed dyspnea using three grades described above within the last 3

days before death.

Clinical symptoms

We then evaluated for pain, fatigue, loss of appetite, insomnia, and dry mouth assessed using the Integrated Palliative Care Outcome Scale (IPOS). IPOS was used to assess symptoms and other concerns of patients with palliative care needs. A higher score indicated a greater intensity (0 = not at all, 1 = slight, 2 = moderate, 3 = severe, and 4 = overwhelming) [21, 22]. Physicians assessed these symptoms by proxy in this study. These symptoms were explored as part of routine examination.

Pleural effusion and ascites

Pleural effusion and ascites were assessed via physical examination and/or X-ray or computed tomography (CT) scan. Pleural effusion and ascites were recorded and categorized into three: without physical findings, with physical findings but asymptomatic, and symptomatic. [20]

Concurrent treatments

Medication (opioids and psychotropic agents, i.e., antipsychotics,

antidepressants, or anxiolytic drugs), volume of fluid infused, blood transfusion, use of antimicrobials, and supplemental oxygen therapy were recorded. Data on types of opioid, route, and oral morphine estimated daily dose were recorded when patients received opioids. Further, the type and dosage of psychotropic agents were recorded.

Definition of development and non-development of dyspnea within 7 days

Any of the following conditions were defined as the development of dyspnea: 1) the presence of dyspnea on exertion or at rest 7 days after admission, 2) patients who received opioids for dyspnea within 7 days after admission, or 3) those who died within 7 days from admission and who had dyspnea on exertion or at rest within 3 days before death. The reason for the development of dyspnea within "7 days" was that our main objective was identifying the predicting factors for the development of dyspnea during early phase after PCU admission. On the other hand, any of the following conditions were defined as the non-development of dyspnea: 1) patients who did not have dyspnea during either the initial or within 7 days of assessment, 2) those who did not receive opioid therapy for dyspnea within 7 days after admission, or 3) those who died within 7 days after admission but did not have dyspnea within 3 days before death. Since there is no existing explanation till date, these definitions were determined by palliative care

specialists via a discussion.

Statistical analysis

Patients were divided into two groups: those who developed dyspnea (development group) and those who did not (non-development group). Next, variables including baseline characteristics, baseline symptoms, and medications were compared between the two groups. Categorical data were analyzed using chi-square test. Continuous variables were analyzed using the *t*-test or the non-parametric Mann–Whitney U test. To identify the factors correlated with newly developed dyspnea, univariate analysis was performed. To determine independent predictive factors, multivariate analysis using the logistic regression model was performed. Analysis was performed using both variables with significant differences in the univariate analysis and factors correlated to worsening dyspnea in previous studies. These factors include old age (>65 years), poor PS (KPS score of <40) [17], primary and metastatic lung cancers [6, 9, 10, 11], chronic respiratory disease [17], and pleural effusion [19]. Finally, to compare two groups, the median survival time was analyzed using the Kaplan–Meier method. A two-tailed p-value of <0.05 was considered statistically significant. Statistical analyses were performed using Statistical Package for the Social Sciences software (SPSS, version 25.0;

IBM, Tokyo, Japan).

Ethics

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and the ethical guidelines for epidemiologic research of the Ministry of Health, Labour and Welfare in Japan. The research was approved by the Institutional Review Boards (IRBs) of Hyogo Prefectural Kakogawa Medical Center (approval no.: 28-8) and the local ethics committee of each participating hospital. The IRBs waived the requirement for written informed consent in this observational study based on the ethical guidelines. Therefore, we used an opt-out method rather than acquiring informed consent. All patients would receive the information of the study at the ward or institutional website, and they had a chance to decline their participation.

Results

From January 2017 to December 2017, 1896 patients were enrolled. Patients who had dyspnea on exertion or at rest on admission (n = 381 and 344, respectively) and those with missing data on dyspnea upon admission or 7 days after admission (n = 12) were excluded. Finally, 1159 patients were included in this analysis (Figure 1). The

characteristics of patients are summarized in Table 1. The most common primary tumor was colorectal cancer (n = 364, 31 %). In total, 200 (17 %) and 344 (30 %) patients presented with pleural effusion and ascites on admission, respectively. Seventy patients developed dyspnea on exertion or at rest 7 days after admission. Twenty-six patients who had dyspnea on exertion or at rest 3 days before death died within 7 days after admission. Four patients received opioids for dyspnea within 7 days after admission. Thus, in total, 100 (5.2 %) patients were included in the development group. The median survival time of the development group was determined to be significantly shorter than that of the non-development group (14 vs. 25 days; $p < 0.001$).

Univariate analysis

The univariate analysis results for both groups are shown in Table 2. Male participants, those with primary lung cancer, ascites, and KPS score of ≤40, smokers, and users of benzodiazepine were significantly higher in the development group than in the non-development group.

Multivariate analysis

Multivariate analysis was performed using factors with significant differences in

the univariate analysis and factors previously reported to be associated with dyspnea. Results showed that primary lung cancer (odds ratio [OR]: 2.80, 95% confidence interval [95% CI]: 1.47–5.31; p = 0.002), KPS score of ≤40 (OR: 1.84, 95% CI: 1.02–3.31; p = 0.044), and presence of ascites (OR: 2.34, 95% CI: 1.36–4.02; p = 0.002) were independent predictive factors for the development of dyspnea (Table 3).

Discussion

Our study has revealed that primary lung cancer, KPS score of ≤40, and ascites can predict the development of dyspnea among terminally ill cancer patients admitted in inpatient hospices/PCUs. Although only a small percentage (5%) of patients developed dyspnea in this study, clinicians should be aware of the possibility of development of dyspnea in patients who have these factors.

Lung parenchyma involvement has been determined to be more common in patients with primary lung cancer than in those with other types of cancers. Invasion to the lung parenchyma might be correlated with the severity of dyspnea. Indeed, several studies have reported an association between lung cancer and severity of dyspnea [6, 9, 10, 11]. This correlation might be associated to increased airway obstruction, lung infection, pleural effusion, reduced lung function and/or ventilator capacity, and increased disassociation

between the need and ability to breathe. This increases the risk of dyspnea at the end-of-life [17, 23]. Hence, clinicians should consider that patients with primary lung cancer admitted to the PCU might develop dyspnea after 7 days even if they do not present with dyspnea upon admission.

Moreover, low KPS score was associated with the development of dyspnea. Ekström et al. reported similar results showing that poor PS is a predictor of worsening dyspnea [17]. Therefore, in patients with poor PS, clinicians should focus on the risk of developing dyspnea.

The novel finding of this study was that ascites was associated with the development of dyspnea. Previous reports have not assessed ascites as a predictor for the development of dyspnea among terminally ill cancer patients. However, several studies have shown an association between ascites and intensity of dyspnea. Ayantunde et al. have revealed that the progression of malignant ascites is associated with dyspnea [24]. Moreover, other reports have shown that dyspnea scores and the 6-min walk test distance significantly improved after paracentesis in patients with liver cirrhosis. [25, 26]. These associations might be attributed to elevated intra-abdominal pressure, which can lead to diaphragmatic elevation. Ascites also restricts full inflation of the respiration, immobilizes the diaphragm, and diminishes the lung volume. These alterations of the respiratory system

may decrease ventilation and V/Q (Ventilation/perfusion) ratio in the basal lung zones [27, 28, 29]. These findings may help explain why ascites was considered a predictive factor for the development of dyspnea in this current study. However, whether ascites was associated with dyspnea could not be determined because this study did not assess the volume of fluid. Therefore, further studies including an assessment of ascites volume should be conducted.

Limitations

This current study has several limitations. First, dyspnea was assessed by a physician, rather than with patient-reported outcome (PRO) measures. This was the most critical limitation. The PRO measures was defined as any report of a patient's health condition obtained directly from the patient without interpretation of responses by a clinician or anyone else. This is an ideal means of systematically assessing a patient's perspective and experience [30]. Therefore, the measurement of PRO measures could be an optimal option; however, in this study, all outcomes were evaluated by physicians owing to the following reasons: (1) this was an observational study of real-world routine clinical practice, not an interventional study. (2) PRO measures may not be obtained in several cases due to the development of cognitive impairment at the end-of-life. Second,

dyspnea was evaluated through invalidated original assessment rather than the use of a quantitative evaluation scale. The original three grades assessment was adopted because only three grades were used for assessment at 7 days after admission, while IPOS and the three grades were used for the initial assessment. Due to this limitation, further research using quantitative and validated assessment tools such as IPOS, a numerical rating scale (NRS), or a visual analogue scale (VAS) is warranted. Third, this multicenter prospective observational study was not designed to acquire continuous data. Hence, information such as daily assessment results from admission to the 7th day of hospitalization was not available. In patients who did not develop dyspnea on both admission and 7 days after admission, we were unable to identify those patients who developed dyspnea during 7 days and who did not receive opioid. Fourth, factors that might have influenced the intensity of dyspnea (such as volume of pleural effusion and ascites on CT scan or ultrasonography, paracentesis for the treatment of pleural effusion, dose and type of opioids, flow rate of supplemental oxygen, and nonpharmacological intervention including chemotherapy, radiation, or tracheal/bronchial stent) were not evaluated. Hence, we could not consider the relationship between dyspnea and these factors. The lack of variables is an important limitation because this is a post-hoc analysis of a prospective observational study.

Implications for clinical practice

Patients with lung cancer and poor PS may develop dyspnea. Therefore, caution should be observed. In addition, clinicians should consider not only abdominal distension caused by increasing volume of ascites but also the development of dyspnea among terminally ill cancer patients. In particular, they should consider selecting morphine over other opioids. The prediction of dyspnea development may be useful in identifying patients with whom end-of-life care should be discussed before their conditions deteriorate.

Conclusions

Lung cancer, poor PS, and ascites may be predictive factors for the development of dyspnea among terminally ill cancer patients. Clinicians should consider that patients with primary lung cancer and poor PS admitted to the PCU might develop dyspnea after 7 days even if they do not present with dyspnea upon admission. Moreover, for patients with ascites, both abdominal distension caused by increasing volume of ascites and development of dyspnea should be considered. Further research that can evaluate dyspnea using validated tools and can assess the volume of ascites and changes over time must be

performed.

Declarations

Ethics approval and Consent to participate: This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and the ethical guidelines for epidemiologic research of the Ministry of Health, Labour and Welfare in Japan. The research was approved by the independent Ethics Committee of Hyogo Prefectural Kakogawa Medical Center (approval no.: 28-8) and the local ethics committee of each participating hospital. A written informed consent was not required, and patients were given the choice to drop out from the study to opt put.

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Authors' contributions:

Conceptualization: Ryo Matsunuma, Takashi Yamaguchi

Methodology: Ryo Matsunuma, Takashi Yamaguchi, Masanori Mori, Tomoo Ikari, Kozue Suzuki, Yoshinobu Matsuda, Yoshihisa Matsumoto, Hiroaki Watanabe

Formal analysis and investigation: Ryo Matsunuma, Takashi Yamaguchi, Masanori

Mori

Writing (original draft preparation): Ryo Matsunuma

Writing (review and editing): Ryo Matsunuma, Takashi Yamaguchi, Masanori Mori, Tomoo Ikari, Kozue Suzuki, Yoshinobu Matsuda, Yoshihisa Matsumoto, Hiroaki Watanabe, Yoshiyuki Kizawa

Supervision: Koji Amano, Rena Kamura, Yoshiyuki Kizawa

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(Department of palliative care Miyazaki Medical Association Hospital), Yu Uneno, M.D. (Department of Therapeutic Oncology, Graduate School of Medicine, Kyoto University), Akira Yoshioka, M.D., Ph.D. (Department of Oncology and Palliative Medicine, Mitsubishi Kyoto Hospital), Shuji Hiramoto, M.D. (Department of Oncology and Palliative Medicine, Mitsubishi Kyoto Hospital), Ayako Kikuchi, M.D. (Department of Oncology and Palliative Medicine, Mitsubishi Kyoto Hospital), Tetsuo Hori, M.D. (Department of Respiratory surgery, Mitsubishi Kyoto Hospital), Yosuke Matsuda, M.D. (Palliative Care Department, St.Luke's International Hospital), Hiroyuki Kohara, M.D., Ph.D. (Hiroshima Prefectural Hospital), Hiromi Fanaki, M.D. (Hiroshima Prefectural Hospital), Keiko Tanaka, M.D., Ph.D. (Department of Palliative Care Tokyo Metropolitan Cancer & Infectious Diseases Center Komagome Hospital), Tina Kamei, M.D. (Department of Palliative Care, NTT Medical Center Tokyo), Yukari Azuma, M.D. (Home Care Clinic Aozora Shin-Matsudo), Teruaki Uno, M.D. (Department of Palliative Medicine, Osaka City General Hospital), Jiro Miyamoto, M.D. (Department of Palliative Medicine, Osaka City General Hospital), Hirofumi Katayama, M.D. (Department of Palliative Medicine, Osaka City General Hospital), Hideyuki Kashiwagi, M.D., MBA. (Aso Iizuka Hospital / Transitional and Palliative Care), Eri Matsumoto, M.D. (Aso Iizuka Hospital / Transitional and Palliative Care), Kiyofumi Oya, M.D. (Aso Iizuka

Hospital / Transitional and Palliative Care), Takeya Yamaguchi, M.D. (Japan Community Health care Organization Kyushu Hospital / Palliative Care), Tomonao Okamura, M.D., MBA. (Aso Iizuka Hospital / Transitional and Palliative Care), Hoshu Hashimoto, M.D., MBA. (Inoue Hospital / Internal Medicine), Shunsuke Kosugi, M.D. (Department of General Internal Medicine, Aso Iizuka Hospital), Nao Ikuta, M.D. (Department of Emergency Medicine, Osaka Red Cross Hospital), Yaichiro Matsumoto, M.D. (Department of Transitional and Palliative Care, Aso Iizuka Hospital), Takashi Ohmori, M.D. (Department of Transitional and Palliative Care, Aso Iizuka Hospital), Takehiro Nakai, M.D. (Immuno-Rheumatology Center, St Luke's International Hospital), Takashi Ikee, M.D. (Department of Cardiorogy, Aso Iizuka Hospital), Yuto Unoki, M.D. (Department of General Internal Medicine, Aso Iizuka Hospital), Kazuki Kitade, M.D. (Department of Orthopedic Surgery, Saga-Ken Medical Centre Koseikan), Shu Koito, M.D. (Department of General Internal Medicine, Aso Iizuka Hospital), Nanao Ishibashi, M.D. (Environmental Health and Safety Division, Environmental Health Department, Ministry of the Environment), Masaya Ehara, M.D. (TOSHIBA), Kosuke Kuwahara, M.D. (Department of General Internal Medicine, Aso Iizuka Hospital), Shohei Ueno, M.D. (Department of Hematology / Oncology, Japan Community Healthcare Organization Kyushu Hospital), Shunsuke Nakashima, M.D. (Oshima Clinic), Yuta

Ishiyama, M.D. (Department of Transitional and Palliative Care, Aso Iizuka Hospital), Akihiro Sakashita, M.D., Ph.D. (Department of Palliative Medicine, Kobe University School of Medicine), , Hana Takatsu, M.D. (Division of Palliative Care, Konan Medical Center), Satoko Ito, M.D. (Hospice, The Japan Baptist Hospital), Toru Terabayashi, M.D. (Hospice, The Japan Baptist Hospital), Jun Nakagawa, M.D. (Hospice, The Japan Baptist Hospital), Tetsuya Yamagiwa, M.D., Ph.D. (Hospice, The Japan Baptist Hospital), Akira Inoue, M.D., Ph.D. (Department of Palliative Medicine Tohoku University School of Medicine), Takuhiro Yamaguchi, Ph.D. (Professor of Biostatistics, Tohoku University Graduate School of Medicine), Mitsunori Miyashita, R.N., Ph.D. (Department of Palliative Nursing, Health Sciences, Tohoku University Graduate School of Medicine), Saran Yoshida, Ph.D. (Graduate School of Education, Tohoku University), Yusuke Hiratsuka, M.D., Ph.D. (Department of Palliative Medicine Tohoku University School of Medicine), Keita Tagami, M.D., Ph.D. (Department of Palliative Medicine Tohoku University School of Medicine), Watanabe Hiroaki, M.D. (Department of Palliative Care, Komaki City Hospital), Odagiri Takuya, M.D. (Department of Palliative Care, Komaki City Hospital), Tetsuya Ito, M.D.,Ph.D. (Department of Palliative Care, Japanese Red Cross Medical Center), Masayuki Ikenaga, M.D. (Hospice, Yodogawa Christian Hospital), Keiji Shimizu, M.D., Ph.D. (Department of Palliative Care Internal Medicine,

Osaka General Hospital of West Japan Railway Company), Akira Hayakawa, M.D., Ph.D. (Hospice, Yodogawa Christian Hospital), , Takeru Okoshi, M.D., Ph.D. (Okoshi Nagominomori Clinic), Isseki Maeda M.D., Ph.D. (Department of Palliative Care, Senri-Chuo Hospital), Tomohiro Nishi, M.D. (Kawasaki Municipal Ida Hospital, Kawasaki Comprehensive Care Center), Kazuhiro Kosugi, M.D. (Department of Palliative Medicine, National Cancer Center Hospital East), Yasuhiro Shibata, M.D. (Kawasaki Municipal Ida Hospital, Kawasaki Comprehensive Care Center), Takayuki Hisanaga, M.D. (Department of Palliative Medicine, Tsukuba Medical Center Hospital), Takahiro Higashibata, M.D., Ph.D. (Department of General Medicine and Primary Care, Palliative Care Team, University of Tsukuba Hospital), Ritsuko Yabuki, M.D. (Department of Palliative Medicine, Tsukuba Medical Center Hospital), Shingo Hagiwara, M.D. (Department of Palliative Medicine, Tsukuba Medical Center Hospital), Miho Shimokawa, M.D. (Department of Palliative Medicine, Tsukuba Medical Center Hospital), Satoshi Miyake, M.D., Ph.D. (Professor, Department of Clinical Oncology Graduate School of Medical and Dental Sciences Tokyo Medical and Dental University (TMDU)), Junko Nozato, M.D. (Specially Appointed Assistant Professor, Department of Internal Medicine, Palliative Care, Medical Hospital, Tokyo Medical and Dental University), Hiroto Ishiki, M.D. (Department of Palliative Medicine, National Cancer

Center Hospital), Tetsuji Iriyama, M.D. (Specially Appointed Assistant Professor, Department of Internal Medicine, Palliative Care, Medical Hospital, Tokyo Medical and Dental University), Keisuke Kaneishi, M.D., Ph.D. (Department of Palliative Care Unit, JCHO Tokyo Shinjuku Medical Center), Mika Baba, M.D., Ph.D. (Department of Palliative medicine Suita Tokushukai Hospital), Tomofumi Miura, M.D., Ph.D. (Department of Palliative Medicine, National Cancer Center Hospital East), Ayumi Okizaki, M.D., Ph.D. (Department of Palliative Medicine, National Cancer Center Hospital East), Yuki Sumazaki Watanabe, M.D. (Department of Palliative Medicine, National Cancer Center Hospital East), Kazuhiro Kosugi, M.D. (Department of Palliative Medicine, National Cancer Center Hospital East), Yuko uehara, M.D. (Department of Palliative Medicine, National Cancer Center Hospital East), Eriko Satomi, M.D. (Department of palliative medicine, National Cancer Center Hospital), Kaoru Nishijima, M.D. (Department of Palliative Medicine, Kobe University Graduate School of Medicine), Junichi Shimoinaba, M.D. (Department of Hospice Palliative Care, Eikoh Hospital), Ryoichi Nakahori, M.D. (Department of Palliative Care, Fukuoka Minato Home Medical Care Clinic), Takeshi Hirohashi, M.D. (Eiju General Hospital), Jun Hamano, M.D., Ph.D. (Assistant Professor, Faculty of Medicine, University of Tsukuba), Natsuki Kawashima, M.D. (Department of Palliative Medicine, Tsukuba Medical Center

Hospital), Takashi Kawaguchi, Ph.D. (Tokyo University of Pharmacy and Life Sciences Department of Practical Pharmacy), Megumi Uchida, M.D., Ph.D. (Dept. of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences), Ko Sato, M.D., Ph.D. (Hospice, Ise Municipal General Hospital), Yoichi Matsuda, M.D., Ph.D. (Department of Anesthesiology & Intensive Care Medicine / Osaka University Graduate School of Medicine), Yutaka Hatano, M.D., Ph.D. (Hospice, Gratia Hospital), Satoru Tsuneto, M.D., Ph.D. (Professor, Department of Human Health Sciences, Graduate School of Medicine, Kyoto University Department of Palliative Medicine, Kyoto University Hospital), Sayaka Maeda, M.D. (Department of Palliative Medicine, Kyoto University Hospital), Hiroyuki Otani, M.D. (Palliative Care Team, and Palliative and Supportive Care, National Kyushu Cancer Center)

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Table 1 Characteristics of patients in the development and non-development groups upon admission

Items	Total (n=1159)	Development group (n=100)	Non-development group (n=1059)
Age (years), mean±SD	72±13	72±13	72±13
Female sex, n (%)	589 (51)	42 (42)	547 (52)
Primary lesion			
Lung, n (%)	142 (12)	20 (20)	122 (12)
Gastrointestinal tract, n (%)	364 (31)	31 (31)	333 (31)
Hepatobiliary system and pancreas, n (%)	250 (22)	14 (14)	236 (22)
Urethra and prostate, n (%)	85 (7.3)	9 (9)	76 (7.2)
Breast, n (%)	62 (5.3)	7 (7)	55 (5.2)
Uterus and ovary, n (%)	65 (5.6)	3 (3)	63 (5.9)
Metastatic lesion			
Liver, n (%)	458 (40)	38 (38)	420 (40)
Bone, n (%)	285 (25)	29 (29)	256 (24)
Lung, n (%)	323 (28)	28 (28)	295 (28)
CNS, n (%)	179 (15)	15 (15)	164 (15)
Comorbidity			
Heart disease, n (%)	56 (4.8)	4 (4)	52 (4.9)
Cerebrovascular disease, n (%)	83 (7.2)	9 (9)	74 (7.0)
Chronic respiratory disease, n (%)	42 (3.6)	3 (3)	39 (3.7)
Chronic liver disease, n (%)	53 (4.6)	3 (3)	50 (4.7)
Chronic kidney disease, n (%)	18 (1.6)	3 (3)	15 (1.4)
Dementia, n (%)	106 (9.1)	11 (11)	95 (9.0)
Smoking, n (%)	380 (3.3)	39 (39)	341 (32)
Performance status			
ECOG PS score, mean±SD	3.3±0.7	3.4±0.7	3.4±0.7
KPS score, mean±SD	40±15	38±13	40±15
Pain intensity based on the IPOS score,	1.5±1.4	1.5±1.4	1.5±1.4

mean±SD			
Edema, n (%)	497 (43)	54 (54)	443 (42)
Ascites, n (%)	344 (30)	40 (40)	304 (29)
Paracentesis for ascites within 7 days after admission, n (%)	42 (3.6)	5 (5)	37 (3.5)
Pleural effusion, n (%)	200 (17)	20 (20)	180 (17)
Supplemental oxygen, n (%)	161 (14)	20 (20)	141 (13)
Opioids			
Morphine, n (%)	112 (9.7)	13 (13)	99 (9.3)
Oxycodone, n (%)	325 (28)	32 (32)	293 (28)
Fentanyl, n (%)	207 (18)	15 (15)	192 (18)
Psychotropic agents			
Benzodiazepine, n (%)	176 (15)	22 (22)	154 (15)
Antidepressant, n (%)	47 (4.1)	4 (4)	43 (4.1)
Survival time, median days		14	25

SD, standard deviation; IPOS, Integrated Palliative Care Outcome Scale; ECOG PS, Eastern Cooperative Oncology Group performance status; KPS, Karnofsky Performance Scale; CNS, central nervous system.

Table 2 Univariate analysis of factors for the development of dyspnea 7 days after admission

Variables	Development group (n=100)	Non-development group (n=1059)	P value
Age ≥65 years, n (%)	73 (73)	820 (77)	0.187
Male sex, n (%)	**58 (58)**	**512 (52)**	**0.041**
Primary lung cancer, n (%)	**20 (20)**	**122 (12)**	**0.014**
Metastatic lung cancer, n (%)	28 (28)	295 (28)	0.531
Chronic pulmonary disease, n (%)	3 (3)	39 (3.7)	0.502
Smoker, n (%)	**39 (39)**	**341 (32)**	**0.045**
Pain (IPOS score of ≥ 2) , n (%)	35 (35)	357 (34)	0.458
Pleural effusion, n (%)	20 (20)	180 (17)	0.262
Ascites, n (%)	**40 (40)**	**304 (29)**	**0.014**
KPS score of ≤40, n (%)	**76 (76)**	**698 (66)**	**0.017**
Morphine, n (%)	13 (13)	99 (9.3)	0.157
Oxycodone, n (%)	32 (32)	293 (28)	0.209
Fentanyl, n (%)	15 (15)	192 (18)	0.264
Benzodiazepine, n (%)	**22 (22)**	**154 (15)**	**0.037**
Antidepressant, n (%)	4 (4)	43 (4.1)	0.617

KPS: Karnofsky Performance Scale; IPOS, Integrated Palliative Care Outcome Scale.

Table 3 Multivariate analysis of factors for the development of dyspnea 7 days after admission

Variables	Odds ratio	95% CI	p value
Primary lung cancer	2.80	1.47–5.31	0.002
KPS score of ≤40	1.84	1.02–3.31	0.044
Presence of ascites	2.34	1.36–4.02	0.002

CI: confidence interval; KPS, Karnofsky Performance Scale.

Figure 1 Study flowchart