



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,...

(Citation)

American Journal of Hospice and Palliative Medicine, 39(4):413-420

(Issue Date)

2022-04

(Resource Type)

journal article

(Version)

Accepted Manuscript

(Rights)

Matsunuma R, Yamaguchi T, Mori M, et al. Predictive Factors for the Development of Dyspnea Within 7 Days After Admission Among Terminally Ill Cancer Patients. American Journal of Hospice and Palliative Medicine®. 2022;39(4):413-420. Copyright © The Author(s) 2021. DOI:10.1177/10499091211028817

(URL)

<https://hdl.handle.net/20.500.14094/0100481872>



American Journal of Hospice and Palliative Medicine

Predictive factors for the development of dyspnea within 7 days after admission among terminally ill cancer patients

Journal:	<i>American Journal of Hospice and Palliative Medicine</i>
Manuscript ID	Draft
Manuscript Type:	Medical Manuscripts
Keyword:	dyspnea, end-of-life, predictors, development, cancer, ascites

SCHOLARONE™
Manuscripts

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

1
2
3
4
5
6 independent predictive factors for the development of dyspnea.
7
8

9 **Conclusions:** Lung cancer, poor performance status, and ascites may be predictive
10 factors for the development of dyspnea among terminally ill cancer patients. However,
11
12 further studies should be performed to validate these findings.
13
14
15
16
17
18
19
20

21 **Keywords:** dyspnea, end-of-life, predictors, development, cancer, ascites
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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/m²) [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

1
2
3
4
5
6 patients have been published. There are two advantages to being able to predict the
7
8 development of dyspnea at the end-of-life. First, for example, if patients require opioids
9
10 for pain management, we can choose morphine with more confidence, which
11
12 demonstrates the highest degree of evidence of effectiveness for dyspnea, provided the
13
14 patients do not suffer from severe renal dysfunction. Second, dyspnea is one of the major
15
16 conditions that can cause distress for terminally ill cancer patients and may require
17
18 sedation for symptom relief. If the development of dyspnea can be predicted, it is possible
19
20 to discuss end-of-life care with the patient in advance, including the desire to use sedation
21
22 therapy, in preparation for the development of dyspnea that is difficult to relieve. This
23
24 current study aimed to identify predictive factors for the development of dyspnea among
25
26 terminally ill cancer patients admitted in inpatient hospices/palliative care units (PCUs).
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4
5
6 study has utilized the data of patients admitted to 23 inpatient hospices/PCUs in Japan.
7
8
9 Consecutive eligible patients were enrolled in the original study if they had been
10
11
12 recently admitted to the participating inpatient hospices/PCUs during the study period.
13
14
15 All interventions and assessments were conducted within routine clinical practice. The
16
17
18 inclusion criteria of this study were as follows: 1) patients aged ≥ 18 years, 2) those
19
20
21 diagnosed with locally extensive or metastatic cancer (including hematological
22
23
24 neoplasms), and 3) those who did not present with dyspnea during the initial evaluation.
25
26
27 Meanwhile, patients who had dyspnea upon admission were excluded.
28
29
30
31
32

33 *Measurement*

34
35
36 All data were prospectively recorded by primary responsible physicians on a
37
38
39 structured data collecting sheet designed and piloted prior to study initiation as a part of
40
41
42 routine practice. These data were recorded starting from admission to inpatient
43
44
45 hospices/PCUs (baseline) till death or discharge. Patient characteristics, clinical
46
47
48 symptoms, vital signs, laboratory findings, pleural effusion and ascites, and concurrent
49
50
51 treatment were evaluated at initial assessment. If the patients did not die within 7 days,
52
53
54 clinical symptoms (dyspnea, insomnia, fatigue, drowsiness, and dry mouth), ascites, and
55
56
57 infused fluid volume were assessed at 7 days after admission. If the patients were
58
59
60

1
2
3
4
5
6 administered opioids for relieving dyspnea, intensity of dyspnea; pleural effusion and
7
8
9 ascites; and opioid type, dosage, and route of administration were assessed. Although
10
11
12 these assessments were not employed in this study, opioid administration for dyspnea
13
14
15 was used as a definition for the development of dyspnea (see details below). Moreover,
16
17
18 if patients died within 7 days after admission, clinical symptoms including dyspnea
19
20
21 were assessed within 3 days before death.
22
23
24
25
26
27

28 *Characteristics of patients*

29
30 Information on age, gender, height, weight, primary and metastatic lesions,
31
32 comorbidities, smoking status, and performance status (PS) (assessed using the Eastern
33
34 Cooperative Oncology Group and Karnofsky Performance Status [KPS]) was evaluated.
35
36
37 Smoking status was categorized into four: none, past, current, or unknown.
38
39
40
41
42
43
44
45

46 *Assessment of dyspnea*

47
48 Dyspnea was classified into three grades: no dyspnea, dyspnea only during
49
50 exertion, and dyspnea at rest [20]. Seven days after admission, physicians evaluated
51
52
53 living patients with dyspnea using the three grades described above. When patients
54
55
56
57 died, physicians assessed dyspnea using three grades described above within the last 3
58
59
60

1
2
3
4
5
6 days before death.
7
8
9

10 11 12 *Clinical symptoms* 13

14
15 We then evaluated for pain, fatigue, loss of appetite, insomnia, and dry mouth
16
17 assessed using the Integrated Palliative Care Outcome Scale (IPOS). IPOS was used to
18
19 assess symptoms and other concerns of patients with palliative care needs. A higher
20
21 score indicated a greater intensity (0 = not at all, 1 = slight, 2 = moderate, 3 = severe,
22
23 and 4 = overwhelming) [21, 22]. Physicians assessed these symptoms by proxy in this
24
25 study. These symptoms were explored as part of routine examination.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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,

1
2
3
4
5
6 antidepressants, or anxiolytic drugs), volume of fluid infused, blood transfusion, use of
7
8
9 antimicrobials, and supplemental oxygen therapy were recorded. Data on types of
10
11
12 opioid, route, and oral morphine estimated daily dose were recorded when patients
13
14
15 received opioids. Further, the type and dosage of psychotropic agents were recorded.
16
17
18
19
20

21
22 *Definition of development and non-development of dyspnea within 7 days*
23

24 Any of the following conditions were defined as the development of dyspnea:
25

26
27 1) the presence of dyspnea on exertion or at rest 7 days after admission, 2) patients who
28
29 received opioids for dyspnea within 7 days after admission, or 3) those who died within
30
31 7 days from admission and who had dyspnea on exertion or at rest within 3 days before
32
33 death. The reason for the development of dyspnea within “7 days” was that our main
34
35 objective was identifying the predicting factors for the development of dyspnea during
36
37 early phase after PCU admission. On the other hand, any of the following conditions
38
39 were defined as the non-development of dyspnea: 1) patients who did not have dyspnea
40
41 during either the initial or within 7 days of assessment, 2) those who did not receive
42
43 opioid therapy for dyspnea within 7 days after admission, or 3) those who died within 7
44
45 days after admission but did not have dyspnea within 3 days before death. Since there is
46
47 no existing explanation till date, these definitions were determined by palliative care
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6 specialists via a discussion.
7
8
9

10 11 12 *Statistical analysis* 13

14
15 Patients were divided into two groups: those who developed dyspnea
16 (development group) and those who did not (non-development group). Next, variables
17 including baseline characteristics, baseline symptoms, and medications were compared
18 between the two groups. Categorical data were analyzed using chi-square test.
19
20 Continuous variables were analyzed using the *t*-test or the non-parametric Mann–Whitney
21 U test. To identify the factors correlated with newly developed dyspnea, univariate
22 analysis was performed. To determine independent predictive factors, multivariate
23 analysis using the logistic regression model was performed. Analysis was performed
24 using both variables with significant differences in the univariate analysis and factors
25 correlated to worsening dyspnea in previous studies. These factors include old age (>65
26 years), poor PS (KPS score of <40) [17], primary and metastatic lung cancers [6, 9, 10,
27 11], chronic respiratory disease [17], and pleural effusion [19]. Finally, to compare two
28 groups, the median survival time was analyzed using the Kaplan–Meier method. A two-
29 tailed p-value of <0.05 was considered statistically significant. Statistical analyses were
30 performed using Statistical Package for the Social Sciences software (SPSS, version 25.0;
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6 IBM, Tokyo, Japan).

7
8
9
10
11
12 *Ethics*

13
14
15 This study was conducted in accordance with the ethical standards of the
16
17 Declaration of Helsinki and the ethical guidelines for epidemiologic research of the
18
19 Ministry of Health, Labour and Welfare in Japan. The research was approved by the
20
21 Institutional Review Boards (IRBs) of Hyogo Prefectural Kakogawa Medical Center
22
23 (approval no.: 28-8) and the local ethics committee of each participating hospital. **The**
24
25 **IRBs waived the requirement for written informed consent in this observational study**
26
27 **based on the ethical guidelines. Therefore, we used an opt-out method rather than**
28
29 **acquiring informed consent. All patients would receive the information of the study at the**
30
31 **ward or institutional website, and they had a chance to decline their participation.**
32
33
34
35
36
37
38
39
40
41
42
43
44

45 *Results*

46
47
48 From January 2017 to December 2017, 1896 patients were enrolled. Patients
49
50 who had dyspnea on exertion or at rest on admission (n = 381 and 344, respectively) and
51
52 those with missing data on dyspnea upon admission or 7 days after admission (n = 12)
53
54 were excluded. Finally, 1159 patients were included in this analysis (Figure 1). The
55
56
57
58
59
60

1
2
3
4
5
6 characteristics of patients are summarized in Table 1. The most common primary tumor
7
8
9 was colorectal cancer (n = 364, 31 %). In total, 200 (17 %) and 344 (30 %) patients
10
11
12 presented with pleural effusion and ascites on admission, respectively. Seventy patients
13
14
15 developed dyspnea on exertion or at rest 7 days after admission. Twenty-six patients who
16
17
18 had dyspnea on exertion or at rest 3 days before death died within 7 days after admission.
19
20
21 Four patients received opioids for dyspnea within 7 days after admission. Thus, in total,
22
23
24 100 (5.2 %) patients were included in the development group. The median survival time
25
26
27 of the development group was determined to be significantly shorter than that of the non-
28
29
30 development group (14 vs. 25 days; $p < 0.001$).
31
32
33
34
35
36
37
38

39 *Univariate analysis*

40 The univariate analysis results for both groups are shown in Table 2. Male
41
42 participants, those with primary lung cancer, ascites, and KPS score of ≤ 40 , smokers, and
43
44
45 users of benzodiazepine were significantly higher in the development group than in the
46
47
48 non-development group.
49
50
51
52
53

54 *Multivariate analysis*

55
56
57 Multivariate analysis was performed using factors with significant differences in
58
59
60

1
2
3
4
5
6 the univariate analysis and factors previously reported to be associated with dyspnea.
7
8
9 Results showed that primary lung cancer (odds ratio [OR]: 2.80, 95% confidence interval
10
11 [95% CI]: 1.47–5.31; $p = 0.002$), KPS score of ≤ 40 (OR: 1.84, 95% CI: 1.02–3.31; $p =$
12
13 0.044), and presence of ascites (OR: 2.34, 95% CI: 1.36–4.02; $p = 0.002$) were
14
15 independent predictive factors for the development of dyspnea (Table 3).
16
17
18
19
20
21
22
23
24

25 *Discussion*

26
27 Our study has revealed that primary lung cancer, KPS score of ≤ 40 , and ascites can
28
29 predict the development of dyspnea among terminally ill cancer patients admitted in
30
31 inpatient hospices/PCUs. Although only a small percentage (5%) of patients developed
32
33 dyspnea in this study, clinicians should be aware of the possibility of development of
34
35 dyspnea in patients who have these factors.
36
37
38
39
40
41

42 Lung parenchyma involvement has been determined to be more common in patients
43
44 with primary lung cancer than in those with other types of cancers. Invasion to the lung
45
46 parenchyma might be correlated with the severity of dyspnea. Indeed, several studies have
47
48 reported an association between lung cancer and severity of dyspnea [6, 9, 10, 11]. This
49
50 correlation might be associated to increased airway obstruction, lung infection, pleural
51
52 effusion, reduced lung function and/or ventilator capacity, and increased disassociation
53
54
55
56
57
58
59
60

1
2
3
4
5
6 between the need and ability to breathe. This increases the risk of dyspnea at the end-of-
7
8
9 life [17, 23]. Hence, clinicians should consider that patients with primary lung cancer
10
11
12 admitted to the PCU might develop dyspnea after 7 days even if they do not present with
13
14
15 dyspnea upon admission.
16

17
18 Moreover, low KPS score was associated with the development of dyspnea. Ekström
19
20
21 et al. reported similar results showing that poor PS is a predictor of worsening dyspnea
22
23
24 [17]. Therefore, in patients with poor PS, clinicians should focus on the risk of developing
25
26
27 dyspnea.
28

29
30 The novel finding of this study was that ascites was associated with the development
31
32
33 of dyspnea. Previous reports have not assessed ascites as a predictor for the development
34
35
36 of dyspnea among terminally ill cancer patients. However, several studies have shown an
37
38
39 association between ascites and intensity of dyspnea. Ayantunde et al. have revealed that
40
41
42 the progression of malignant ascites is associated with dyspnea [24]. Moreover, other
43
44
45 reports have shown that dyspnea scores and the 6-min walk test distance significantly
46
47
48 improved after paracentesis in patients with liver cirrhosis. [25, 26]. These associations
49
50
51 might be attributed to elevated intra-abdominal pressure, which can lead to diaphragmatic
52
53
54 elevation. Ascites also restricts full inflation of the respiration, immobilizes the
55
56
57 diaphragm, and diminishes the lung volume. These alterations of the respiratory system
58
59
60

1
2
3
4
5
6 may decrease ventilation and V/Q (Ventilation/perfusion) ratio in the basal lung zones
7
8
9 [27, 28, 29]. These findings may help explain why ascites was considered a predictive
10
11
12 factor for the development of dyspnea in this current study. However, whether ascites
13
14
15 was associated with dyspnea could not be determined because this study did not assess
16
17
18 the volume of fluid. Therefore, further studies including an assessment of ascites volume
19
20
21 should be conducted.
22
23
24
25
26

27 *Limitations*

28
29
30 This current study has several limitations. First, dyspnea was assessed by a
31
32
33 physician, rather than with patient-reported outcome (PRO) measures. This was the most
34
35
36 critical limitation. The PRO measures was defined as any report of a patient's health
37
38
39 condition obtained directly from the patient without interpretation of responses by a
40
41
42 clinician or anyone else. This is an ideal means of systematically assessing a patient's
43
44
45 perspective and experience [30]. Therefore, the measurement of PRO measures could be
46
47
48 an optimal option; however, in this study, all outcomes were evaluated by physicians
49
50
51 owing to the following reasons: (1) this was an observational study of real-world routine
52
53
54 clinical practice, not an interventional study. (2) PRO measures may not be obtained in
55
56
57 several cases due to the development of cognitive impairment at the end-of-life. Second,
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

1
2
3
4
5
6
7
8
9
10 *Implications for clinical practice*

11
12 Patients with lung cancer and poor PS may develop dyspnea. Therefore, caution
13 should be observed. In addition, clinicians should consider not only abdominal distension
14 caused by increasing volume of ascites but also the development of dyspnea among
15 terminally ill cancer patients. In particular, they should consider selecting morphine over
16 other opioids. The prediction of dyspnea development may be useful in identifying
17 patients with whom end-of-life care should be discussed before their conditions
18 deteriorate.
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35

36 **Conclusions**

37
38 Lung cancer, poor PS, and ascites may be predictive factors for the development
39 of dyspnea among terminally ill cancer patients. Clinicians should consider that patients
40 with primary lung cancer and poor PS admitted to the PCU might develop dyspnea after
41 7 days even if they do not present with dyspnea upon admission. Moreover, for patients
42 with ascites, both abdominal distension caused by increasing volume of ascites and
43 development of dyspnea should be considered. Further research that can evaluate dyspnea
44 using validated tools and can assess the volume of ascites and changes over time must be
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6 performed.

7
8
9 ***Declarations***

10
11
12 **Ethics approval and Consent to participate:** This study was conducted in accordance
13
14
15 with the ethical standards of the Declaration of Helsinki and the ethical guidelines for
16
17
18 epidemiologic research of the Ministry of Health, Labour and Welfare in Japan. The
19
20
21 research was approved by the independent Ethics Committee of Hyogo Prefectural
22
23
24 Kakogawa Medical Center (approval no.: 28-8) and the local ethics committee of each
25
26
27 participating hospital. A written informed consent was not required, and patients were
28
29
30 given the choice to drop out from the study to opt put.
31

32
33 **Consent for publication:** Not applicable.
34

35
36 **Competing interests:** The authors declare that they have no competing interests.
37

38
39 **Funding:** This study was supported in part by a Grant-in-Aid from the Japan Hospice
40
41
42 Palliative Care Foundation.
43

44
45 **Authors' contributions:**

46
47
48 Conceptualization: Ryo Matsunuma, Takashi Yamaguchi
49

50
51
52 Methodology: Ryo Matsunuma, Takashi Yamaguchi, Masanori Mori, Tomoo Ikari,
53
54
55 Kozue Suzuki, Yoshinobu Matsuda, Yoshihisa Matsumoto, Hiroaki Watanabe
56

57
58
59 Formal analysis and investigation: Ryo Matsunuma, Takashi Yamaguchi, Masanori
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

Acknowledgments

This study was performed in the East-Asian collaborative cross-cultural Study to Elucidate the Dying process (EASED). The participating study sites and site investigators in Japan were as follows: Satoshi Inoue, M.D. (Seirei Hospice, Seirei Mikatahara General Hospital), Naosuke Yokomichi, M.D., Ph.D. (Department of Palliative and Supportive Care, Seirei Mikatahara General Hospital), Kengo Imai, M.D. (Seirei Hospice, Seirei Mikatahara General Hospital), Tatsuya Morita, M.D. (Department of Palliative and Supportive Care, Seirei Mikatahara General Hospital), Hiroaki Tsukuura, M.D., Ph.D. (Department of Palliative Care, TUMS Urayasu Hospital), Toshihiro Yamauchi, M.D. (Seirei Hospice, Seirei Mikatahara General Hospital), Akemi Shirado Naito, M.D.

1
2
3
4
5
6 (Department of palliative care Miyazaki Medical Association Hospital), Yu Uneno, M.D.
7
8
9 (Department of Therapeutic Oncology, Graduate School of Medicine, Kyoto University),
10
11
12 Akira Yoshioka, M.D., Ph.D. (Department of Oncology and Palliative Medicine,
13
14
15 Mitsubishi Kyoto Hospital), Shuji Hiramoto, M.D. (Department of Oncology and
16
17
18 Palliative Medicine, Mitsubishi Kyoto Hospital), Ayako Kikuchi, M.D. (Department of
19
20
21 Oncology and Palliative Medicine, Mitsubishi Kyoto Hospital), Tetsuo Hori, M.D.
22
23
24 (Department of Respiratory surgery, Mitsubishi Kyoto Hospital), Yosuke Matsuda, M.D.
25
26
27 (Palliative Care Department, St.Luke's International Hospital), Hiroyuki Kohara, M.D.,
28
29
30 Ph.D. (Hiroshima Prefectural Hospital), Hiromi Fanaki, M.D. (Hiroshima Prefectural
31
32
33 Hospital), Keiko Tanaka, M.D., Ph.D. (Department of Palliative Care Tokyo
34
35
36 Metropolitan Cancer & Infectious Diseases Center Komagome Hospital), Tina Kamei,
37
38
39 M.D. (Department of Palliative Care, NTT Medical Center Tokyo), Yukari Azuma, M.D.
40
41
42 (Home Care Clinic Aozora Shin-Matsudo), Teruaki Uno, M.D. (Department of Palliative
43
44
45 Medicine, Osaka City General Hospital), Jiro Miyamoto, M.D. (Department of Palliative
46
47
48 Medicine, Osaka City General Hospital), Hirofumi Katayama, M.D. (Department of
49
50
51 Palliative Medicine, Osaka City General Hospital), Hideyuki Kashiwagi, M.D., MBA.
52
53
54 (Aso Iizuka Hospital / Transitional and Palliative Care), Eri Matsumoto, M.D. (Aso
55
56
57 Iizuka Hospital / Transitional and Palliative Care), Kiyofumi Oya, M.D. (Aso Iizuka
58
59
60

1
2
3
4
5
6 Hospital / Transitional and Palliative Care), Takeya Yamaguchi, M.D. (Japan Community
7
8
9 Health care Organization Kyushu Hospital / Palliative Care), Tomonao Okamura, M.D.,
10
11
12 MBA. (Aso Iizuka Hospital / Transitional and Palliative Care), Hoshu Hashimoto, M.D.,
13
14
15 MBA. (Inoue Hospital / Internal Medicine), Shunsuke Kosugi, M.D. (Department of
16
17
18 General Internal Medicine, Aso Iizuka Hospital), Nao Ikuta, M.D. (Department of
19
20
21 Emergency Medicine, Osaka Red Cross Hospital), Yaichiro Matsumoto, M.D.
22
23
24 (Department of Transitional and Palliative Care, Aso Iizuka Hospital), Takashi Ohmori,
25
26
27 M.D. (Department of Transitional and Palliative Care, Aso Iizuka Hospital), Takehiro
28
29
30 Nakai, M.D. (Immuno-Rheumatology Center, St Luke's International Hospital), Takashi
31
32
33 Ikee, M.D. (Department of Cardiorogy, Aso Iizuka Hospital), Yuto Unoki, M.D.
34
35
36 (Department of General Internal Medicine, Aso Iizuka Hospital), Kazuki Kitade, M.D.
37
38
39 (Department of Orthopedic Surgery, Saga-Ken Medical Centre Koseikan), Shu Koito,
40
41
42 M.D. (Department of General Internal Medicine, Aso Iizuka Hospital), Nanao Ishibashi,
43
44
45 M.D. (Environmental Health and Safety Division, Environmental Health Department,
46
47
48 Ministry of the Environment), Masaya Ehara, M.D. (TOSHIBA), Kosuke Kuwahara,
49
50
51 M.D. (Department of General Internal Medicine, Aso Iizuka Hospital), Shohei Ueno,
52
53
54 M.D. (Department of Hematology / Oncology, Japan Community Healthcare
55
56
57 Organization Kyushu Hospital), Shunsuke Nakashima, M.D. (Oshima Clinic), Yuta
58
59
60

1
2
3
4
5
6
7 Ishiyama, M.D. (Department of Transitional and Palliative Care, Aso Iizuka Hospital),
8
9 Akihiro Sakashita, M.D., Ph.D. (Department of Palliative Medicine, Kobe University
10
11 School of Medicine), , Hana Takatsu, M.D. (Division of Palliative Care, Konan Medical
12
13 Center), Satoko Ito, M.D. (Hospice, The Japan Baptist Hospital), Toru Terabayashi, M.D.
14
15 (Hospice, The Japan Baptist Hospital), Jun Nakagawa, M.D. (Hospice, The Japan Baptist
16
17 Hospital), Tetsuya Yamagiwa, M.D., Ph.D. (Hospice, The Japan Baptist Hospital), Akira
18
19 Inoue, M.D., Ph.D. (Department of Palliative Medicine Tohoku University School of
20
21 Medicine), Takuhiro Yamaguchi, Ph.D. (Professor of Biostatistics, Tohoku University
22
23 Graduate School of Medicine), Mitsunori Miyashita, R.N., Ph.D. (Department of
24
25 Palliative Nursing, Health Sciences, Tohoku University Graduate School of Medicine),
26
27 Saran Yoshida, Ph.D. (Graduate School of Education, Tohoku University), Yusuke
28
29 Hiratsuka, M.D., Ph.D. (Department of Palliative Medicine Tohoku University School of
30
31 Medicine), Keita Tagami, M.D., Ph.D. (Department of Palliative Medicine Tohoku
32
33 University School of Medicine), Watanabe Hiroaki, M.D. (Department of Palliative Care,
34
35 Komaki City Hospital), Odagiri Takuya, M.D. (Department of Palliative Care, Komaki
36
37 City Hospital), Tetsuya Ito, M.D., Ph.D. (Department of Palliative Care, Japanese Red
38
39 Cross Medical Center), Masayuki Ikenaga, M.D. (Hospice, Yodogawa Christian
40
41 Hospital), Keiji Shimizu, M.D., Ph.D. (Department of Palliative Care Internal Medicine,
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6 Osaka General Hospital of West Japan Railway Company), Akira Hayakawa, M.D., Ph.D.
7
8
9 (Hospice, Yodogawa Christian Hospital), , Takeru Okoshi, M.D., Ph.D. (Okoshi
10
11
12 Nagominomori Clinic), Isseki Maeda M.D., Ph.D. (Department of Palliative Care, Senri-
13
14
15 Chuo Hospital), Tomohiro Nishi, M.D. (Kawasaki Municipal Ida Hospital, Kawasaki
16
17
18 Comprehensive Care Center), Kazuhiro Kosugi, M.D. (Department of Palliative
19
20
21 Medicine, National Cancer Center Hospital East), Yasuhiro Shibata, M.D. (Kawasaki
22
23
24 Municipal Ida Hospital, Kawasaki Comprehensive Care Center), Takayuki Hisanaga,
25
26
27 M.D. (Department of Palliative Medicine, Tsukuba Medical Center Hospital), Takahiro
28
29
30 Higashibata, M.D., Ph.D. (Department of General Medicine and Primary Care, Palliative
31
32
33 Care Team, University of Tsukuba Hospital), Ritsuko Yabuki, M.D. (Department of
34
35
36 Palliative Medicine, Tsukuba Medical Center Hospital), Shingo Hagiwara, M.D.
37
38
39 (Department of Palliative Medicine, Tsukuba Medical Center Hospital), Miho
40
41
42 Shimokawa, M.D. (Department of Palliative Medicine, Tsukuba Medical Center
43
44
45 Hospital), Satoshi Miyake, M.D., Ph.D. (Professor, Department of Clinical Oncology
46
47
48 Graduate School of Medical and Dental Sciences Tokyo Medical and Dental University
49
50
51 (TMDU)), Junko Nozato, M.D. (Specially Appointed Assistant Professor, Department of
52
53
54 Internal Medicine, Palliative Care, Medical Hospital, Tokyo Medical and Dental
55
56
57 University), Hiroto Ishiki, M.D. (Department of Palliative Medicine, National Cancer
58
59
60

1
2
3
4
5
6 Center Hospital), Tetsuji Iriyama, M.D. (Specially Appointed Assistant Professor,
7
8
9 Department of Internal Medicine, Palliative Care, Medical Hospital, Tokyo Medical and
10
11
12 Dental University), Keisuke Kaneishi, M.D., Ph.D. (Department of Palliative Care Unit,
13
14
15 JCHO Tokyo Shinjuku Medical Center), Mika Baba, M.D., Ph.D. (Department of
16
17
18 Palliative medicine Suita Tokushukai Hospital), Tomofumi Miura, M.D., Ph.D.
19
20
21 (Department of Palliative Medicine, National Cancer Center Hospital East), Ayumi
22
23
24 Okizaki, M.D., Ph.D. (Department of Palliative Medicine, National Cancer Center
25
26
27 Hospital East), Yuki Sumazaki Watanabe, M.D. (Department of Palliative Medicine,
28
29
30 National Cancer Center Hospital East), Kazuhiro Kosugi, M.D. (Department of Palliative
31
32
33 Medicine, National Cancer Center Hospital East), Yuko uehara, M.D. (Department of
34
35
36 Palliative Medicine, National Cancer Center Hospital East), Eriko Satomi, M.D.
37
38
39 (Department of palliative medicine, National Cancer Center Hospital), Kaoru Nishijima,
40
41
42 M.D. (Department of Palliative Medicine, Kobe University Graduate School of
43
44
45 Medicine), Junichi Shimoinaba, M.D. (Department of Hospice Palliative Care, Eikoh
46
47
48 Hospital), Ryoichi Nakahori, M.D. (Department of Palliative Care, Fukuoka Minato
49
50
51 Home Medical Care Clinic), Takeshi Hirohashi, M.D. (Eiju General Hospital), Jun
52
53
54 Hamano, M.D., Ph.D. (Assistant Professor, Faculty of Medicine, University of Tsukuba),
55
56
57 Natsuki Kawashima, M.D. (Department of Palliative Medicine, Tsukuba Medical Center
58
59
60

1
2
3
4
5
6 Hospital), Takashi Kawaguchi, Ph.D. (Tokyo University of Pharmacy and Life Sciences
7
8
9 Department of Practical Pharmacy), Megumi Uchida, M.D., Ph.D. (Dept. of Psychiatry
10
11
12 and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical
13
14
15 Sciences), Ko Sato, M.D., Ph.D. (Hospice, Ise Municipal General Hospital), Yoichi
16
17
18 Matsuda, M.D., Ph.D. (Department of Anesthesiology & Intensive Care Medicine / Osaka
19
20
21 University Graduate School of Medicine), Yutaka Hatano, M.D., Ph.D. (Hospice, Gratia
22
23
24 Hospital), Satoru Tsuneto, M.D., Ph.D. (Professor, Department of Human Health
25
26
27 Sciences, Graduate School of Medicine, Kyoto University Department of Palliative
28
29
30 Medicine, Kyoto University Hospital), Sayaka Maeda, M.D. (Department of Palliative
31
32
33 Medicine, Kyoto University Hospital), Hiroyuki Otani, M.D. (Palliative Care Team, and
34
35
36 Palliative and Supportive Care, National Kyushu Cancer Center)
37
38
39
40
41
42
43
44

45 *References*

- 46
47
48 1. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et
49
50
51 al. An Official American Thoracic Society Statement: Update on The Mechanisms,
52
53
54 Assessment, and Management of Dyspnea. *Am J Respir Crit Care Med.*
55
56
57 2012;185(4):435–452.
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
2. Bruera E, Schmitz B, Pither J, Neumann CM, Hanson J. The Frequency and Correlates of Dyspnea in Patients With Advanced Cancer. *J Pain Symptom Manage*. 2000 May;19(5):357–362.
3. Nishino T, Shimoyama N, Ide T, Isono S. Experimental Pain Augments Experimental Dyspnea, but Not Vice Versa in Human Volunteers. *Anesthesiology*. 1999 Dec;91(6):1633–1638.
4. Iyer S, Roughley A, Rider A, Taylor-Stokes G. The Symptom Burden of Non-Small Cell Lung Cancer in the USA: A Real-World Cross-Sectional Study. *Support Care Cancer*. 2014 Jan;22(1):181–187.
5. Krug K, Miksch A, Peters-Klimm F, Engeser P, Szecsenyi J. Correlation Between Patient Quality of Life in Palliative Care and Burden of Their Family Caregivers: A Prospective Observational Cohort Study. *BMC Palliat Care*. 2016 Jan 15;15:4.
6. Muers MF, Round CE. Palliation of Symptoms in Non-Small Cell Lung Cancer: A Study by the Yorkshire Regional Cancer Organisation Thoracic Group. *Thorax*. 1993 Apr;48(4):339–343.
7. Currow DC, Smith JM, Chansriwong P, Noble SIR, Nikolaidou T, Ferreira D, et al. Missed Opportunity? Worsening Breathlessness as a Harbinger of Death: A Cohort Study. *Eur Respir J*. 2018 Sep 6;52(3):1800684.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
8. Campbell ML, Kiernan JM, Strandmark J, Yarandi HN. Trajectory of Dyspnea and Respiratory Distress Among Patients in the Last Month of Life. *J Palliat Med.* 2018 Feb;21(2):194–199.
9. Bausewein C, Booth S, Gysels M, Kühnbach R, Haberland B, Higginson IJ. Individual Breathlessness Trajectories Do Not Match Summary Trajectories in Advanced Cancer and Chronic Obstructive Pulmonary Disease: Results From a Longitudinal Study. *Palliat Med.* 2010 Dec;24(8):777–786.
10. Currow DC, Smith J, Davidson PM, Newton PJ, Agar MR, Abernethy AP. Do the Trajectories of Dyspnea Differ in Prevalence and Intensity by Diagnosis at the End of Life? A Consecutive Cohort Study. *J Pain Symptom Manage.* 2010 Apr;39(4):680–690.
11. Edmonds P, Higginson I, Altmann D, Sen-Gupta G, McDonnell M. Is the Presence of Dyspnea a Risk Factor for Morbidity in Cancer Patients? *J Pain Symptom Manage.* 2000;19(1):15–22.
12. Dudgeon DJ, Lertzman M. Dyspnea in the Advanced Cancer Patient. *J Pain Symptom Manage.* 1998;16(4):212–219.
13. Weingaertner V, Scheve C, Gerdes V, Schwarz-Eywill M, Prenzel R, Bausewein C, et al. Breathlessness, Functional Status, Distress, and Palliative Care Needs Over

- 1
2
3
4
5
6 Time in Patients With Advanced Chronic Obstructive Pulmonary Disease or Lung
7
8
9 Cancer: A Cohort Study. *J Pain Symptom Manage.* 2014;48(4):569–581.
10
11
12 14. Ahmadi Z, Lundström S, Janson C, Strang P, Emtner M, Currow DC, et al. End-of-
13
14 life Care in Oxygen-Dependent COPD and Cancer: A National Population-Based
15
16 Study. *Eur Respir J.* 2015 Oct;46(4):1190–1193.
17
18
19
20
21 15. Dudgeon DJ, Kristjanson L, Sloan JA, Lertzman M, Clement K. Dyspnea in Cancer
22
23 Patients: Prevalence and Associated Factors. *J Pain Symptom Manage.* 2001
24
25 Feb;21(2):95–102.
26
27
28
29
30 16. Seow H, Barbera L, Sutradhar R, Howell D, Dudgeon D, Atzema C, et al. Trajectory
31
32 of Performance Status and Symptom Scores for Patients With Cancer During the Last
33
34 Six Months of Life. *J Clin Oncol* 2011;29(9):1151–1158.
35
36
37
38
39 17. Ekström M, Johnson MJ, Schiöler L, Kaasa S, Hjerstad MJ, Currow DC. Who
40
41 Experiences Higher and Increasing Breathlessness in Advanced Cancer? The
42
43 Longitudinal EPCCS Study. *Support Care Cancer.* 2016;24(9):3803–3811.
44
45
46
47
48 18. Santos M, Kitzman DW, Matsushita K, Loehr L, Sueta CA, Shah AM. Outcomes and
49
50 Mortality in Persons Without Prevalent Cardiopulmonary Disease: The
51
52 Atherosclerosis Risk in Communities Study. *PLoS One.* 2016 Oct
53
54 25;11(10):e0165111.
55
56
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
19. Yoshino K, Nishiumi N, Masuda R, Saito Y, Tokuda Y, Iwazaki M. Assessment of
Dyspnea in Terminally Ill Cancer Patients: Role of the Thoracic Surgeon as a
Palliative Care Physician. *Gan To Kagaku Ryoho*. 2011 May;38(5):803–806.
20. Morita T, Tsunoda J, Inoue S, Chihara S. The Palliative Prognostic Index:
A Scoring System for Survival Prediction of Terminally Ill Cancer Patients. *Support
Care Cancer*. 1999;7(3):128–133.
21. Beck I, Möller UO, Malmström M, Klarare A, Samuelsson H, Hagelin CL, et al.
Translation and Cultural Adaptation of the Integrated Palliative Care Outcome Scale
Including Cognitive Interviewing With Patients and Staff. *BMC Palliat Care*. 2017
Sep 11;16(1):49.
22. Schildmann EK, Groeneveld EI, Denzel J, Brown A, Bernhardt F, Bailey K, et al.
Discovering the Hidden Benefits of Cognitive Interviewing in Two Languages: The
First Phase of a Validation Study of the Integrated Palliative Care Outcome Scale.
Palliat Med. 2016;30(6):599–610.
23. Dyspnea and Its Correlates in Taiwanese Patients With Terminal Cancer. *J Pain
Symptom Manage*. 2004;28(2):123–132.
24. Ayantunde AA, Parsons SL. Pattern and Prognostic Factors in
Patients With Malignant Ascites: A Retrospective Study. *Ann Oncol*

- 2007;18(05):945–949.
25. Wittmer VL, Lima RT, Maia MC, Duarte H, Paro FM. Respiratory and Symptomatic Impact of Ascites Relief by Paracentesis in Patients With Hepatic Cirrhosis. *Arq Gastroenterol.* 2020;57(1):64–68.
26. Makhoulf NA, Mahran ZG, Sadek SH, Magdy DM, Makhoulf HA. Six-minute Walk Test Before and After Large-Volume Paracentesis in Cirrhotic Patients With Refractory Ascites: A Pilot Study. *Arab J Gastroenterol.* 2019 Jun;20(2):81–85.
27. Yao EH, Kong B, Hsue G, Zhou A, Wang H. Pulmonary Function Changes in Cirrhosis of the Liver. *Am J Gastroenterol.* 1987;82(4):352–354.
28. Nitrini MA, Stirbulov R, Rolim EG. Influence of Ascites in the Pulmonary Function of Patients With Portal Hypertension. *J Bras Pneumol.* 2004;30:14–19.
29. Chang SC, Chang HI, Chen FJ, Shiao GM, Wang SS, Lee SD. Therapeutic effects of diuretics and paracentesis on lung function in patients with non-alcoholic cirrhosis and tense ascites. *J Hepatol.* 1997 Apr;26(4):833-8.
30. Patrick DL, Burke LB, Powers JH, Scott JA, Rock EP, Dawisha S, et al. Patient-reported Outcomes to Support Medical Product Labeling Claims: FDA Perspective. *Value Health.* Nov-Dec 2007;10 Suppl 2:S125–S137.

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 \geq 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 \geq 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 \leq40, 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.

For Peer Review

Figure 1 Study flowchart

