

**Brief Report**

# The Current Practice of Opioid for Cancer Dyspnea: The Result From the Nationwide Survey of Japanese Palliative Care Physicians



Takashi Yamaguchi, MD, PhD, Ryo Matsunuma, MD, Kozue Suzuki, MD, Yoshinobu Matsuda, MD, Masanori Mori, MD, and Hiroaki Watanabe, MD

*Division of Palliative Care (T.Y.), Department of Medicine, Konan Hospital, Kobe; Department of Palliative Medicine (R.M.), Kobe University Graduate School of Medicine, Kobe; Department of Palliative Care (K.S.), Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, Tokyo; Department of Psychosomatic Internal Medicine (Y.M.), Kinki-Chuo Chest Medical Center, Sakai; Palliative Care Team (M.M.), Seirei Mikatahara General Hospital, Hamamatsu; and Department of Palliative Care (H.W.), Komaki City Hospital, Komaki, Japan*

**Abstract**

**Context.** Morphine is recommended as the first-line pharmacological therapy for cancer dyspnea. However, the detailed practice of morphine has not been evaluated and consensus about other opioids for cancer dyspnea has not been established.

**Objectives.** To explore the physician-reported practice of opioid for cancer dyspnea.

**Methods.** A nationwide mail-questionnaire survey was conducted among 536 Japanese certified palliative care physicians. We randomly selected 268 and asked the following: 1) how the physicians themselves initiate and use morphine for cancer dyspnea, 2) opioid choice for dyspnea in patients who have already used opioid other than morphine regularly, and 3) opioid choice for dyspnea in patients with various degrees of renal impairment in their daily practice.

**Results.** Overall, 192 physicians responded (response rate, 71.6%). The major (58.3%) practice of initiating morphine was “immediate-release morphine as needed” in opioid-naïve patients, and the mean % increase when they titrate morphine for cancer dyspnea was  $29.4 \pm 11.3\%$  of the baseline dose. Although “titrate baseline oxycodone” was the most frequent (42.3%) for low-to-moderate-dose regular oxycodone cases, “stepwise switch to morphine” (30.0%) and “add morphine on baseline oxycodone” (27.1%) were the more frequent practices for high-dose regular oxycodone. Regardless of the baseline dose, “add morphine on baseline fentanyl” was the most frequent practice for regular transdermal fentanyl cases. Oxycodone was the most frequent choice in renal insufficiency cases, regardless of its degree.

**Conclusions.** Among Japanese palliative care physicians, using oxycodone for cancer dyspnea was relatively popular practice, whereas fentanyl was not. Oxycodone was the most preferred opioid for cancer dyspnea in the setting of renal insufficiency among Japanese palliative care physicians. We should conduct studies to confirm the safety and effectiveness of these opioid practices for cancer dyspnea. *J Pain Symptom Manage* 2019;58:672–677. © 2019 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

**Key Words**

*Dyspnea, cancer, opioid, morphine, oxycodone, hydromorphone, fentanyl*

**Introduction**

Dyspnea is defined as “a subjective experience of breathing discomfort.”<sup>1</sup> It is a common symptom in patients with advanced cancer, with a reported

prevalence of 54%–76%,<sup>2–5</sup> and one of the most distressing symptoms for not only patients but also their families and caregivers.

Systemic morphine is the only pharmacological therapy proven to be efficacious for cancer dyspnea.<sup>6–9</sup> In

*Address correspondence to:* Takashi Yamaguchi, MD, PhD, Division of Palliative Care, Department of Internal Medicine, Konan Hospital, 1-5-16, Kamokogahara, Higashi-Nada, Kobe 658-0064, Japan. E-mail: [ikagoro@pop06.odn.ne.jp](mailto:ikagoro@pop06.odn.ne.jp)

*Accepted for publication:* June 5, 2019.

addition, it is recommended as the first-line pharmacological treatment by several clinical guidelines.<sup>10–14</sup> However, a detailed practice, such as the method of starting and titrating opioid, has not been covered by these guidelines. Moreover, insufficient evidence or conflicting results about the efficacy of other opioids for cancer dyspnea, such as oxycodone,<sup>15–18</sup> hydromorphone,<sup>19,20</sup> and fentanyl were noted.<sup>21–25</sup> Based on the paucity of clear-cut evidence, existing guidelines do not give any conclusive recommendations on the use of opioid other than morphine for cancer dyspnea.<sup>14,26</sup> In clinical practice, physicians often face the situations in which morphine use is controversial or contraindicated, such as in renal impairment cases, when they see patients with advanced cancer. However, currently, there is no consensus whether a physician should use morphine for cancer dyspnea even in such situations. In addition, physicians may take different approaches about opioid for the patient with cancer developing dyspnea when the patient has already used opioid other than morphine for pain. Thus, a wide variation of opioid prescription practice for cancer dyspnea may exist in current real-world practice.

As the first step for standardizing opioid practice for cancer dyspnea, we explore the current practice of opioid for dyspnea in patients with cancer among Japanese palliative care physicians.

## Methods

We conducted a nationwide survey that used an anonymous, self-reported questionnaire. This study was approved by the institutional review board of Konan Hospital.

### Participants

We identified a total of 536 certified palliative care physicians from the website of the Japanese Society for Palliative Medicine as potential participants for this questionnaire survey. We divided them into two groups by a random selection of 268 (half of 536). We sent a questionnaire about the dyspnea management in ambulatory patients with cancer to one group and another about the dyspnea management in patients with cancer at the end of life to the other group. The topic we present here was included in a questionnaire about the dyspnea management in ambulatory patients with cancer. The results of other topics we surveyed will be presented elsewhere.

### Procedure

We sent a questionnaire to potential participants via postal mail on September 2018 and asked them to complete and return the questionnaire within one

month. A remainder was sent to nonresponders one month after the first questionnaire had been sent.

### Measurements

Because of the lack of an existing specific questionnaire, we developed ad hoc questionnaires based on the literature review, discussion among palliative care specialists, and result of pilot testing on palliative care fellows. We set a theoretical scenario who met the following conditions: adult ambulatory patient with cancer, expected survival more than several months, and dyspnea of 2 to 3 modified Medical Research Council scale. We asked about the daily opioid practice for dyspnea in this theoretical case. Except where mentioned, the patient could take medications orally and would not have renal and liver dysfunction and allergy or other contraindications to any opioids.

*How the Physicians Initiate and Use Morphine for Cancer Dyspnea.* We asked about the method of initiating oral morphine for dyspnea in opioid-naïve patients with cancer. Each option was rated using the five-point Likert scale (1, rarely; 2, seldom; 3, sometimes; 4, often; and 5, very often). Furthermore, we queried what percentage of the dose of regular morphine the participants usually increased at one time when they titrated morphine for cancer dyspnea and whether they had the upper-limit dosage of morphine, and if they had, how much was the upper limit of daily morphine dosage.

*Opioid Choice for Dyspnea in Patients Who Have Already Used Opioid Other Than Morphine Regularly.* We asked about the usual opioid practice for dyspnea when patients had already taken regular oxycodone or fentanyl for cancer pain. We separately asked about the setting of low-to-moderate (<80 mg/day) and high (>120 mg/day) doses of oxycodone and low (25 µg/hour), moderate (50 µg/hour), and high (100 µg/hour) doses of transdermal fentanyl. We set the following options for the regular oral oxycodone scenario: titrate baseline oxycodone, add morphine on baseline oxycodone, partial replace to morphine, stepwise switch to morphine, immediate switch to morphine, and switch to fentanyl. Furthermore, the following are for the regular transdermal fentanyl scenario: titrate baseline fentanyl, add morphine on baseline fentanyl, partial replace to morphine, stepwise switch to morphine, and immediate switch to morphine. Each option was rated using the five-point Likert scale, the same as mentioned earlier. We only set the setting of oral oxycodone and transdermal fentanyl cases because morphine and these two agents are the most popular opioid analgesics for cancer pain.

*Opioid Choice for Dyspnea in Patients With Various Degrees of Renal Impairment.* We asked about the opioid choice for dyspnea in opioid-naïve patients with various degrees of renal insufficiency. We separately asked about the setting of moderate renal insufficiency (eGFR, 10–30 mL/minute/1.73 m<sup>3</sup>) and severe renal insufficiency (eGFR < 10 mL/minute/1.73 m<sup>3</sup>) with and without renal replacement therapy (RRT). We set the following options: morphine, oxycodone, hydromorphone, and fentanyl. Each option was again rated using the five-point Likert scale same as mentioned earlier.

### Statistical Analysis

All data were managed and analyzed using SPSS for Windows software, version 19.0 (IBM Japan Institute, Tokyo, Japan). All data presented here were analyzed in a descriptive manner. The proportions of “often” or “very often” do a certain practice were calculated with 95% confidence intervals (CIs). We also calculated a mean value of % increase of basal morphine for dyspnea. In addition, we calculated the proportion of physicians who had the upper-limit dosage of morphine for dyspnea with 95% CI and a mean value of the upper-limit dosage.

## Results

A total of 192 physicians returned the questionnaires, and all were included to the analysis (response rate, 71.6%).

### *How the Physicians Initiate and Use Morphine for Cancer Dyspnea*

The initiation of oral “immediate-release morphine as needed” was the most frequent practice (58.3%; 95% CI, 51.4–65.3) among the participating palliative care physicians, followed by “control-release morphine regularly” (22%; 95% CI, 16.1–27.9) and “immediate-release morphine regularly” (12.6%; 95% CI, 7.9–17.3). The mean % increase from baseline was 29.4% ± 11.3% when they titrate morphine for cancer dyspnea. Only 36.5% (95% CI, 30.0–43.4)

of participants reported they had the upper limit of morphine for dyspnea, and their mean upper-limit dose of morphine was 119.9 ± 132.9 mg/day.

### *Opioid Choice for Dyspnea in Patients Who Have Already Used Opioid Other Than Morphine Regularly*

Although the majority of participants (42.3%; 95% CI, 35.3–49.3) reported that they frequently or very frequently “titrate baseline oxycodone” for the scenario involving those who have already used a low-to-moderate dose of regular oxycodone, “stepwise switch to morphine” (30.0%; 95% CI, 23.5–36.5) and “add morphine on baseline oxycodone” (27.1%; 95% CI, 20.8–33.4) were the more frequent practices than “titrate baseline oxycodone” (19.6%; 95% CI, 13.9–25.2) for those who have a high dose of regular oxycodone (Table 1).

For the scenario involving those who have already used regular transdermal fentanyl (Table 2), “add morphine on baseline fentanyl” was the most frequent practice among participants regardless of the dose of fentanyl (41.6% [95% CI, 34.6–48.6] for low-dose fentanyl, 39.6% [95% CI, 32.7–46.5] for the moderate dose, and 37.5% [95% CI, 30.7–44.4] for the high dose). On the other hand, the proportion of “stepwise switch to morphine” increased as the dose of baseline fentanyl increased (25.7% [95% CI, 19.5–31.9] for low-dose fentanyl, 35.4% [95% CI, 28.6–42.3] for the moderate dose, and 37.9% [95% CI, 31.0–44.8] for the high dose).

### *Opioid Choice for Dyspnea in Patients With Various Degrees of Renal Impairment*

Participants were prescribed oxycodone for cancer dyspnea most frequently regardless of the degree of renal insufficiency (56.0% [95% CI, 49.0–63.1] for moderate renal insufficiency, 57.6% [95% CI, 50.6–64.6] for severe renal insufficiency without RRT, and 45.2% [95% CI, 38.1–52.3] for severe renal insufficiency with RRT). The second most frequent agent was hydromorphone for all renal insufficiency scenarios (36.6% [95% CI, 28.4–44.9] for moderate renal insufficiency, 34.1% [95% CI, 25.9–42.3] for severe renal insufficiency without RRT, and

Table 1  
Opioid Choice for Dyspnea in Patients on Regular Oral Oxycodone

	On Low-Moderate-Dose Regular Oxycodone [% (95% CI)]	On High-Dose Regular Oxycodone [% (95% CI)]
Titrate baseline oxycodone	42.3 (35.3–49.4)	19.6 (13.9–25.2)
Add morphine on baseline oxycodone	16.8 (11.5–22.2)	27.1 (20.8–33.4)
Partial replace to morphine	6.8 (3.2–10.4)	14.3 (9.3–19.3)
Stepwise switch to morphine	21.6 (15.7–27.4)	30.0 (23.5–36.5)
Immediate switch to morphine	11.1 (6.6–15.5)	5.3 (2.1–8.5)
Switch to fentanyl	1.6 (–0.2 to 3.4)	1.7 (–0.2–3.4)

Table 2  
Opioid Choice for Dyspnea in Patients on Regular Transdermal Fentanyl

	On Low-Dose Regular Fentanyl [% (95% CI)]	On Moderate-Dose Regular Fentanyl [% (95% CI)]	On High-Dose Regular Fentanyl [% (95% CI)]
Titrate baseline fentanyl	4.7 (1.7–7.8)	4.2 (1.4–7.1)	2.6 (0.4–4.9)
Add morphine on baseline fentanyl	41.6 (34.6–48.6)	39.6 (32.7–46.5)	35.7 (30.7–44.4)
Partial replace to morphine	10.5 (6.2–14.9)	13.7 (8.8–18.6)	19.5 (13.8–25.1)
Stepwise switch to morphine	25.7 (19.5–31.9)	35.4 (28.6–42.3)	37.9 (31.0–44.8)
Immediate switch to morphine	23.2 (17.2–29.2)	7.9 (4.1–11.8)	3.7 (1.0–6.4)

29.6% [95% CI, 21.6–37.6] for severe renal insufficiency with RRT) (Table 3).

### Discussion

This is, to the best of our knowledge, the first report about a detailed practice of opioid for cancer dyspnea among palliative care specialists.

The first major finding was that starting immediate-release preparation as needed was the most prevalent practice of morphine for dyspnea in opioid-naïve patients with cancer among Japanese palliative care specialists. In addition, we found that Japanese palliative care physicians titrated morphine with about 30% increase of baseline. This is consistent with the result of the previous study on cancer dyspnea.<sup>6</sup> Furthermore, the majority (63.5%) of them used morphine without a limit dose unless any adverse event related to morphine had not developed. These results suggest that Japanese palliative care physicians proactively increase the morphine dosage if it is not sufficiently effective in patients who are in relatively good condition. This is conflict with the previous study reporting that most of “chronic dyspnea” responded to 30 mg/day or less of morphine.<sup>27</sup> Another study suggested that high dose of morphine (more than 30 mg/day) might adversely affected the mortality.<sup>28</sup> However, these data were mostly about patients with chronic obstructive pulmonary disease, and higher dose of morphine was used in studies of cancer dyspnea.<sup>7–9</sup> Thus, there may be the difference in response to

morphine between dyspnea in patients with cancer and population without cancer including chronic obstructive pulmonary disease. However, because no confirmatory data are described, we have to conduct researches investigating the best practice of titrating morphine for cancer dyspnea in terms of the safety and effectiveness.

The second major finding was that Japanese palliative care specialists increase baseline oxycodone for dyspnea first in the patients who have already used regular oxycodone. However, they shift their practice to using morphine more for dyspnea if the patients have already used a high dose of oxycodone. This result suggests that Japanese palliative care specialists think oxycodone as somewhat effective for cancer dyspnea. However, they tend to follow more rigid evidence (the effectiveness of morphine for cancer dyspnea)<sup>7,9</sup> when a higher dose of oxycodone is not sufficiently effective possibly because there are only suggestive but insufficient evidence of oxycodone for cancer dyspnea.<sup>15,18</sup> On the other hand, they appear to think fentanyl as ineffective. This may be because the results of the studies of fentanyl for prophylaxis of exertional dyspnea are inconsistent<sup>21–25</sup> and the evidence for resting dyspnea is insufficient.<sup>29,30</sup> It may be simpler and safer if we can manage both pain and dyspnea by a single agent in a same drug class (opioid) because the combination use of different opioids has potential disadvantages, such as complexity in handling medications for both patients and health-care providers and facing the risk of adverse events from different medications. Therefore, further

Table 3  
Opioid Choice for Dyspnea in Patients With Renal Insufficiency

	Moderate Renal Insufficiency [% (95% CI)]	Severe Renal Insufficiency Without RRT [% (95% CI)]	Severe Renal Insufficiency With RRT [% (95% CI)]
Morphine	16.8 (11.5–22.1)	2.6 (0.4–4.9)	8.0 (4.1–11.9)
Oxycodone	56.0 (49.0–63.0)	57.6 (50.6–64.6)	45.2 (38.1–52.3)
Hydromorphone	36.6 (28.4–44.9)	34.1 (25.9–42.3)	29.6 (21.6–37.6)
Fentanyl	5.3 (2.1–8.5)	7.9 (4.1–11.8)	11.2 (6.7–15.8)

RRT = renal replacement therapy.

research to confirm the effectiveness of opioids other than morphine is warranted.

The third major finding was oxycodone was the most prevalent opioid agent for cancer dyspnea in the setting of renal insufficiency regardless of its severity, which was followed by hydromorphone. Some opioids, such as fentanyl, buprenorphine, and methadone, have been reported as the “safer” opioids in the setting of renal insufficiency.<sup>31–33</sup> However, the evidence and experience of these opioids for cancer dyspnea have been scarce. Several reports of the relative safety of oxycodone and hydromorphone in the patients with renal insufficiency compared with morphine are noted.<sup>32</sup> Combined with relative safety in renal insufficiency and the suggestive effectiveness of oxycodone<sup>15,17,18</sup> and hydromorphone<sup>19,20</sup> for cancer dyspnea, Japanese palliative care specialists may choose these agents for dyspnea in cancer patients with renal insufficiency. However, this practice has not been confirmed as safe in well-designed researches. Thus, we should use these opioids in renal insufficiency cases with careful monitoring of adverse events. Moreover, the more rigid evidence that shows data on safety of oxycodone or hydromorphone in patients with renal insufficiency is needed.

This study has several limitations. First, this is the survey of physician-reported practice and some differences between the result of this study and their actual practice may be noted. Thus, the survey of the actual practice should be investigated. Second, because we just showed the physician-reported major opioid practice for cancer dyspnea, the safety and effectiveness of these practices have not been confirmed. Thus, as we mentioned earlier, future prospective studies that confirm the safety and effectiveness of opioid practices presented here are needed. Third, the results of this study are based only on Japanese palliative care specialists’ opinion. Thus, these may not be generalized outside Japan and more data from the international perspective are needed. Fourth, our questionnaire did not include detailed background information of participants. This was to minimize the burden of participants to respond lengthy questionnaires and maximize the response rate. Our primary intention was not to explore the difference in opioid practice for cancer dyspnea between different background groups but the Japanese palliative care specialists’ practice in general. Thus, it was more important to achieve a higher response rate, and actually, we did (more than 70%). However, it is possible that participants’ background affects the style of practices. Thus, our results may not be generalized.

In conclusion, among Japanese palliative care physicians, using oxycodone for cancer dyspnea was a relatively popular practice, whereas using fentanyl was not. Oxycodone was the most preferred opioid for cancer

dyspnea in the setting of renal insufficiency among Japanese palliative care physicians. To standardize the best possible opioid practice for cancer dyspnea, we should conduct more rigid studies that will clarify the most effective titration strategy, the efficacy of opioids other than morphine, and the safety and effectiveness of opioids including morphine in the setting of renal insufficiency for cancer dyspnea in the future.

### **Disclosures and Acknowledgments**

The authors thank Dr. Tatsuya Morita and Dr. Keiko Tanaka for their advices for conducting this study.

This study was supported by a Grant-in-Aid for Young Scientists of the Ministry of Education, Culture, Sports, Science and Technology of Japan (18K15389).

The authors declare no conflicts of interest.

### **References**

1. Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012;185:435–452.
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;19:357–362.
3. Chiu TY, Hu WY, Lue BH, Yao CA, Chen CY, Wakai S. Dyspnea and its correlates in Taiwanese patients with terminal cancer. *J Pain Symptom Manage* 2004;28:123–132.
4. Reuben DB, Mor V. Dyspnea in terminally ill cancer patients. *Chest* 1986;89:234–236.
5. Skaug K, Eide GE, Gulsvik A. Prevalence and predictors of symptoms in the terminal stage of lung cancer: a community study. *Chest* 2007;131:389–394.
6. Allard P, Lamontagne C, Bernard P, Tremblay C. How effective are supplementary doses of opioids for dyspnea in terminally ill cancer patients? A randomized continuous sequential clinical trial. *J Pain Symptom Manage* 1999;17:256–265.
7. Bruera E, MacEachern T, Ripamonti C, Hanson J. Subcutaneous morphine for dyspnea in cancer patients. *Ann Intern Med* 1993;119:906–907.
8. Bruera E, Macmillan K, Pither J, MacDonald RN. Effects of morphine on the dyspnea of terminal cancer patients. *J Pain Symptom Manage* 1990;5:341–344.
9. Mazzocato C, Buclin T, Rapin CH. The effects of morphine on dyspnea and ventilatory function in elderly patients with advanced cancer: a randomized double-blind controlled trial. *Ann Oncol* 1999;10:1511–1514.
10. Ben-Aharon I, Gafter-Gvili A, Leibovici L, Stemmer SM. Interventions for alleviating cancer-related dyspnea: a systematic review and meta-analysis. *Acta Oncologica* 2012;51:996–1008.
11. Ben-Aharon I, Gafter-Gvili A, Paul M, Leibovici L, Stemmer SM. Interventions for alleviating cancer-related dyspnea: a systematic review. *J Clin Oncol* 2008;26:2396–2404.

12. Dy SM, Lorenz KA, Naeim A, Sanati H, Walling A, Asch SM. Evidence-based recommendations for cancer fatigue, anorexia, depression, and dyspnea. *J Clin Oncol* 2008;26:3886–3895.
13. Qaseem A, Snow V, Shekelle P, et al. Evidence-based interventions to improve the palliative care of pain, dyspnea, and depression at the end of life: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2008;148:141–146.
14. Yamaguchi T, Goya S, Kohara H, et al. Treatment recommendations for respiratory symptoms in cancer patients: clinical guidelines from the Japanese Society for palliative medicine. *J Palliat Med* 2016;19:925–935.
15. Kawabata M, Kaneishi K. Continuous subcutaneous infusion of compound oxycodone for the relief of dyspnea in patients with terminally ill cancer: a retrospective study. *Am J Hosp Palliat Care* 2013;30:305–311.
16. Shinjo T, Okada M. [Efficacy of controlled-release oxycodone for dyspnea in cancer patients—three case series]. *Gan To Kagaku Ryoho* 2006;33:529–532.
17. Yamaguchi T, Matsuda Y, Matsuoka H, et al. Efficacy of immediate-release oxycodone for dyspnea in cancer patient: cancer dyspnea relief (CDR) trial. *Jpn J Clin Oncol* 2018;48:1070–1075.
18. Yamamoto Y, Watanabe H, Sakurai A, et al. Effect of continuous intravenous oxycodone infusion in opioid-naïve cancer patients with dyspnea. *Jpn J Clin Oncol* 2018;48:748–752.
19. Charles MA, Reymond L, Israel F. Relief of incident dyspnea in palliative cancer patients: a pilot, randomized, controlled trial comparing nebulized hydromorphone, systemic hydromorphone, and nebulized saline. *J Pain Symptom Manage* 2008;36:29–38.
20. Clemens KE, Klaschik E. Effect of hydromorphone on ventilation in palliative care patients with dyspnea. *Support Care Cancer* 2008;16:93–99.
21. Hui D, Kilgore K, Frisbee-Hume S, et al. Effect of prophylactic fentanyl buccal tablet on episodic exertional dyspnea: a pilot double-blind randomized controlled trial. *J Pain Symptom Manage* 2017;54:798–805.
22. Hui D, Kilgore K, Park M, Williams J, Liu D, Bruera E. Impact of prophylactic fentanyl pectin nasal spray on exercise-induced episodic dyspnea in cancer patients: a double-blind, randomized controlled trial. *J Pain Symptom Manage* 2016;52:459–468.e1.
23. Hui D, Xu A, Frisbee-Hume S, et al. Effects of prophylactic subcutaneous fentanyl on exercise-induced breakthrough dyspnea in cancer patients: a preliminary double-blind, randomized, controlled trial. *J Pain Symptom Manage* 2014;47:209–217.
24. Pinna MA, Bruera E, Moralo MJ, Correas MA, Vargas RM. A randomized crossover clinical trial to evaluate the efficacy of oral transmucosal fentanyl citrate in the treatment of dyspnea on exertion in patients with advanced cancer. *Am J Hosp Palliat Care* 2015;32:298–304.
25. Simon ST, Kloke M, Alt-Epping B, et al. EffenDys-fentanyl buccal tablet for the relief of episodic breathlessness in patients with advanced cancer: a multicenter, open-label, randomized, morphine-controlled, crossover, phase II trial. *J Pain Symptom Manage* 2016;52:617–625.
26. Kloke M, Cherny N. Treatment of dyspnea in advanced cancer patients: ESMO clinical practice guidelines. *Ann Oncol* 2015;26(Suppl 5):v169–v173.
27. Currow DC, McDonald C, Oaten S, et al. Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *J Pain Symptom Manage* 2011;42:388–399.
28. Ekstrom MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ* 2014;348:g445.
29. Simon ST, Köskeroglu P, Gaertner J, Voltz R. Fentanyl for the relief of refractory breathlessness: a systematic review. *J Pain Symptom Manage* 2013;46:874–886.
30. Barnes H, McDonald J, Smallwood N, Manser R. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database Syst Rev* 2016;3:CD011008.
31. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage* 2004;28:497–504.
32. King S, Forbes K, Hanks GW, Ferro CJ, Chambers EJ. A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project. *Palliat Med* 2011;25:525–552.
33. Murtagh FE, Chai MO, Donohoe P, Edmonds PM, Higginson IJ. The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. *J Pain Palliat Care Pharmacother* 2007;21:5–16.

## Appendix

Please choose your daily practices of oral or transdermal opioids for dyspnea (modified Medical Research Council scale 2–3) in ambulatory adult patients with cancer with life expectancy of months or more.

\* Assume that the patient could take medications orally and would not have renal and liver dysfunction or allergies/other contraindications to any opioids, unless specified otherwise.

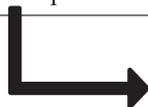
	Rarely	Seldom	Sometimes	Often	Very Often
How do you initiate oral morphine for newly developed dyspnea in an <b>opioid-naïve patient with cancer</b> ?					
Pro re nata (as needed) immediate-release morphine (1~5 mg/dose)	1	2	3	4	5
Start immediate-release morphine (1~5 mg) regularly (2~6 times daily)	1	2	3	4	5
Start control release morphine (10~20 mg/day)	1	2	3	4	5

- (1) How much do you usually increase the dose of morphine for dyspnea in a patient with cancer who has already used 30–100 mg/day of regular oral morphine?

Increase by (                      ) %

- (2) Which of the following better fits your practice when administering morphine for dyspnea in patients with cancer?

- 1 . Titrate (increase) morphine without an upper limit, unless any adverse effects develop
- 2 . Set the upper limit of morphine for dyspnea even if no adverse effect develops



The upper limit in your practice: (                      ) mg/day

	Rarely	Seldom	Sometimes	Often	Very Often
How do you initiate oral morphine for newly developed dyspnea in an <b>opioid-naïve patient with cancer</b> ?					
Pro re nata (as needed) immediate-release morphine (1~5 mg/dose)	1	2	3	4	5
Start immediate-release morphine (1~5 mg) around the clock (2~6 times daily)	1	2	3	4	5
Start control release morphine (10~20 mg/day)	1	2	3	4	5
How do you manage opioids for newly developed dyspnea in a patient with cancer who has already used regular low-dose oral oxycodone (less than 80 mg/day) for pain?					
Titrate (increase the dose of) baseline oxycodone	1	2	3	4	5
Add morphine on baseline oxycodone	1	2	3	4	5
Partially replace oxycodone with morphine	1	2	3	4	5
Switch oxycodone to morphine, stepwise	1	2	3	4	5
Switch oxycodone to morphine, immediately	1	2	3	4	5
Switch oxycodone to transdermal fentanyl	1	2	3	4	5
How do you manage opioids for newly developed dyspnea in a patient with cancer who has already used regular high-dose oral oxycodone (more than 120 mg/day) for pain?					
Titrate (increase the dose of) baseline oxycodone	1	2	3	4	5
Add morphine on baseline oxycodone	1	2	3	4	5
Partially replace oxycodone with morphine	1	2	3	4	5
Switch oxycodone to morphine, stepwise	1	2	3	4	5
Switch oxycodone to morphine, immediately	1	2	3	4	5
Switch oxycodone to transdermal fentanyl	1	2	3	4	5

(Continued)

## Continued

	Rarely	Seldom	Sometimes	Often	Very Often
How do you manage opioids for newly developed dyspnea in a patient with cancer who has already used regular low-dose transdermal fentanyl (25 µg/hour) for pain?					
Titrate (increase the dose of) baseline fentanyl	1	2	3	4	5
Add oral morphine on baseline fentanyl	1	2	3	4	5
Partially replace fentanyl with oral morphine	1	2	3	4	5
Switch fentanyl to oral morphine, stepwise	1	2	3	4	5
Switch oxycodone to oral morphine, immediately	1	2	3	4	5
How do you manage opioids for newly developed dyspnea in a patient with cancer who has already used regular moderate-dose transdermal fentanyl (50 µg/hour) for pain?					
Titrate (increase the dose of) baseline fentanyl	1	2	3	4	5
Add oral morphine on baseline fentanyl	1	2	3	4	5
Partially replace fentanyl with oral morphine	1	2	3	4	5
Switch fentanyl to oral morphine, stepwise	1	2	3	4	5
Switch oxycodone to oral morphine, immediately	1	2	3	4	5
How do you manage opioids for newly developed dyspnea in a patient with cancer who has already used regular high-dose transdermal fentanyl (100 µg/hour) for pain?					
Titrate (increase the dose of) baseline fentanyl	1	2	3	4	5
Add oral morphine on baseline fentanyl	1	2	3	4	5
Partially replace fentanyl with oral morphine	1	2	3	4	5
Switch fentanyl to oral morphine, stepwise	1	2	3	4	5
Switch oxycodone to oral morphine, immediately	1	2	3	4	5
Which opioid do you usually choose for dyspnea in an opioid-naïve cancer patient with moderate renal insufficiency (estimated glomerular filtration ratio 10~30 mL/minute/1.73 m <sup>3</sup> )?					
Morphine	1	2	3	4	5
Oxycodone	1	2	3	4	5
Fentanyl	1	2	3	4	5
Hydromorphone	1	2	3	4	5
Which opioid do you usually choose for dyspnea in an opioid-naïve cancer patient with severe renal insufficiency (estimated glomerular filtration ratio < 10 mL/minute/1.73 m <sup>3</sup> ) but not on renal replacement therapy?					
Morphine	1	2	3	4	5
Oxycodone	1	2	3	4	5
Fentanyl	1	2	3	4	5
Hydromorphone	1	2	3	4	5
Which opioid do you usually choose for dyspnea in an opioid-naïve cancer patient with severe renal insufficiency (estimated glomerular filtration ratio < 10 mL/minute/1.73 m <sup>3</sup> ) on renal replacement therapy?					
Morphine	1	2	3	4	5
Oxycodone	1	2	3	4	5
Fentanyl	1	2	3	4	5
Hydromorphone	1	2	3	4	5