

Original Article

Cite this article: Hatano Y *et al.* (2021). Complexity of desire for hastened death in terminally ill cancer patients: A cluster analysis. *Palliative and Supportive Care* 19, 646–655. <https://doi.org/10.1017/S1478951521000080>

Received: 2 September 2020

Revised: 17 December 2020




Accepted: 7 February 2021

Key words:

Cluster analysis; Desire for hastened death; Multicentre observational study; Reasons of desire for death; Terminally ill cancer patients

Author for correspondence: Yutaka Hatano, Department of Palliative Care, Daini Kyoritsu Hospital, Kawanishi, Japan.

E-mail: yutakahatano1@gmail.com

Yutaka Hatano, M.D., PH.D.¹ , Tatsuya Morita, M.D.², Masanori Mori, M.D.³, Isseki Maeda, M.D., PH.D.⁴, Shunsuke Oyamada, M.Sc.⁵, Akemi Shirado Naito, M.D.⁶, Kiyofumi Oya, M.D.⁷, Akihiro Sakashita, M.D., PH.D.⁸ , Satoko Ito, M.D.⁹, Yusuke Hiratsuka, M.D., PH.D.¹⁰ , Satoru Tsuneto, M.D., PH.D.¹¹ and on behalf of the EASED Investigators¹

¹Department of Palliative Care, Daini Kyoritsu Hospital, Kawanishi, Japan; ²Palliative and Supportive Care Division, Seirei Mikatahara General Hospital, Hamamatsu, Japan; ³Palliative Care Team, Seirei Mikatahara General Hospital, Hamamatsu, Japan; ⁴Department of Palliative Care, Senri Chuo Hospital, Osaka, Japan; ⁵Department of Biostatistics, JORTC Data Center, Tokyo, Japan; ⁶Department of Palliative Care, Miyazaki Medical Association Hospital, Miyazaki, Japan; ⁷Transitional and Palliative Care, Aso Iizuka Hospital, Fukuoka, Japan; ⁸Department of Palliative Medicine, Kobe University School of Medicine, Kobe, Japan; ⁹Hospice, The Japan Baptist Hospital, Kyoto, Japan; ¹⁰Department of Palliative Medicine, Tohoku University School of Medicine, Sendai, Japan and ¹¹Department of Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Abstract

Objectives. The present study aims were (1) to identify the proportion of terminally ill cancer patients with desire for hastened death (DHD) receiving specialized palliative care, (2) to identify the reasons for DHD, and (3) to classify patients with DHD into some interpretable subgroups. **Methods.** Advanced cancer patients admitted to 23 inpatient hospices/palliative care units in 2017 were enrolled. Data were prospectively obtained by the primarily responsible physicians. The presence/absence of DHD and reasons for DHD were recorded. A cluster analysis was performed to identify patterns of subgroups in patients with DHD.

Results. Data from 971 patients, whose Richmond Agitation–Sedation Scale score at admission was zero and who died in palliative care units, were analyzed. The average age was 72 years, common primary cancer sites were the gastrointestinal tract (31%) and the liver/biliary ducts/pancreas (19%). A total of 174 patients (18%: 95% confidence interval, 16–20) expressed DHD. Common reasons for DHD were dependency (45%), burden to others (28%), meaninglessness (24%), and inability to engage in pleasant activities (24%). We identified five clusters of patients with DHD: cluster 1 (35%, 61/173): “physical distress,” cluster 2 (21%, 37/173): “dependent and burdensome,” cluster 3 (19%, 33/173): “hopelessness,” cluster 4 (17%, 30/173): “profound fatigue,” and cluster 5 (7%, 12/173): “extensive existential suffering.”

Conclusions. A considerable number of patients expressed DHD and could be categorized into five subgroups. These findings may contribute to the development of therapeutic strategies.

Introduction

A desire for hastened death (DHD) is one of the most serious problems in terminally ill cancer patients. DHD is defined as a reaction to suffering in the context of a life-threatening condition, from which the patient may believe there is no other way to cope than to accelerate his/her death (Balaguer *et al.*, 2016). Several studies indicate that 17–44% of advanced cancer patients have DHD at least occasionally, and 1.5–12% of them have severe DHD (Chochinov *et al.*, 1995; Breitbart *et al.*, 2000; Morita *et al.*, 2004; Rodin *et al.*, 2007; Wilson *et al.*, 2016). Both quantitative and qualitative data show many reasons and factors related to DHD. Depression is often reported as one of the most important factors of DHD (Chochinov *et al.*, 1995; Breitbart *et al.*, 2000; O’Mahony *et al.*, 2005; Villavicencio-Chávez *et al.*, 2014; Parpa *et al.*, 2019). In recent studies, demoralization which is distinct from depression has been shown as an important mediator of suicidal thoughts and DHD (Robinson *et al.*, 2017; Vehling *et al.*, 2017). Existential distress (e.g., loss of autonomy and meaninglessness) (McClain *et al.*, 2003; Morita *et al.*, 2004; Mystakidou *et al.*, 2006) and physical symptoms (e.g., pain and dyspnea) are also predictors of DHD (Breitbart *et al.*, 2000). Recent trends toward legalization of euthanasia and physician-assisted suicide (PAS) have highlighted the need for more information about DHD. The presence of severe and consistent DHD is associated with requests for euthanasia and PAS (Chochinov *et al.*, 1995; Breitbart *et al.*, 2000; Morita *et al.*, 2004; Wilson *et al.*, 2016). There may be common reasons and factors related to the desire for euthanasia/PAS and DHD in terminally ill cancer patients (Ganzini *et al.*, 2002, 2008; Suarez-Almazor *et al.*, 2002; Wilson *et al.*,

2007). As DHD may be associated with a wide range of distress, the assessment and management of DHD are essential skills for palliative care professionals.

Previous studies have shown that patients have different coexisting factors associated with DHD (Morita et al., 2004; Wilson et al., 2007). The expression of DHD often indicates underlying multidimensional distress. Although there have been many observational studies of terminally ill cancer patients with DHD (Chochinov et al., 1995; Breitbart et al., 2000; Morita et al., 2004), common patterns of coexisting factors remain unclear. These complex phenomena make it difficult for palliative care professionals to manage DHD.

Cluster analysis is a widely used statistical method that classifies cases into similar patterns of subgroups and has been used in many research areas (Eisen et al., 1998; Logan et al., 2011; Lochner et al., 2019). However, to our knowledge, no empirical studies have adopted this method to palliative cancer patients with DHD. The aims of the present study were (1) to identify the proportion of terminally ill cancer patients with DHD, (2) to identify the reasons for DHD, and (3) to identify common patterns of subgroups in terminally ill cancer patients with DHD.

Methods

Procedure

This was part of a multicentre observational study. Participants were terminally ill cancer patients admitted to 23 palliative care units (PCUs) throughout Japan during January 2017–June 2018. Patients were consecutively enrolled, but in the specific periods, when the research was not performed due to practical reasons, e.g., unavailability of researchers on certain days of the week, over the weekends or holidays, or due to staff rotations, we allowed each institution to skip patient enrollment for the specific periods and the numbers of the patients were recorded. Those aged 17 years or less were excluded. Patients who planned to be discharged within 1 week or those who did not want to be enrolled were also excluded. This study was conducted in accordance with the ethical standards of the Helsinki Declaration and the ethical guidelines for epidemiological research presented by the Ministry of Health, Labour and Welfare in Japan. This was a noninvasive observational study. Written consent was waived according to the guideline, as all interventions were performed within routine clinical practice, each patient had no additional burden (e.g., no questionnaires needed to be completed by patients), and obtaining the information from all patients was vital for this study aim (selection of the consented patients would lead to the lack of validity of this study). The study protocol was approved by the research ethics committees of all institutions involved in the study.

Variables

The primarily responsible physician most involved with the patient obtained prospective data from daily clinical practice. Demographic data, including age, sex, marital status, religion, past illness history, current medication, and primary cancer site, were obtained from patients' medical charts. Consciousness level at admission was assessed using the Modified Richmond Agitation–Sedation Scale (RASS) (Imai et al., 2016). Eastern Cooperative Oncology Group (ECOG) performance status (Oken et al., 1982) and palliative performance status (PPS; Anderson et al., 1996) at admission were

assessed by the primarily responsible physician. Cognitive function was assessed using the Abbreviated Mental Test (Hodkinson, 1972). Physical and psychological symptoms were assessed using the Integrated Palliative care Outcome Scale (IPOS; Sakurai et al., 2019). Patients' awareness and preparedness were assessed using the Good Death Scale (GDS; Yao et al., 2007). We categorized the reason why the patient chose to enter a PCU according to a list of potential reasons that we developed, referring to a previous study (Gomes et al., 2012). Medical procedures such as opioid prescriptions and the presence or absence of initiation of continuous deep sedation (CDS) were recorded.

Desire for hastened death

Similar to our previous study, the presence of DHD was defined as patient's expressions of DHD to family member or medical professionals during the patient's stay at the PCU (Morita et al., 2004). Reasons for DHD were also recorded depending on the statements of patients. From a list of possible reasons we developed, we selected the main 12 reasons, referring to previous studies (Chochinov et al., 1995; Ganzini et al., 2002; Morita et al., 2004; Wilson et al., 2007, 2016). The reasons included (1) dependency, (2) burden to others, (3) loss of autonomy, (4) meaninglessness/loss of value, (5) inability to engage in any pleasant activities, (6) hopelessness, (7) loneliness, (8) dyspnea, (9) pain, (10) other physical symptoms, (11) fear of death, (12) profound fatigue, and (13) no specific reasons. The presence or absence of an explicit wish for administration of lethal drugs was also recorded (Chochinov et al., 1995; Morita et al., 2004; Wilson et al., 2016). In Japan, physician-assisted suicide and euthanasia are illegal, but some patients expressed their strong desire for earlier death using this term.

The presence/absence of DHD and reasons for DHD were evaluated by a primarily responsible palliative care specialist after a patient's death. Although we had acknowledged the limitation of the proxy rating, we had decided to adapt this method on the assumption that palliative care specialists examine the patients at least once a day, usually two times or more (morning and evening), every day during the in-patient care periods. Furthermore, an interdisciplinary conference is held among healthcare workers at PCUs. Participating physicians from all the study sites attended an orientation session to review the study objectives and data collection forms. Moreover, the principal investigator and lead investigators at each site provided longitudinal support during the study period to ensure accurate and complete data collection. To examine proxy bias, we planned to explore the concordance of physician ratings with bereaved family's ratings in a post-bereavement survey. Bereaved family survey demonstrated acceptable concordance between physician-reported and family-reported prevalence of desire for hastened death ($\kappa = 0.50$ among 458 family members responded, unpublished data).

Statistical analysis

Of the patients who died in PCUs, data from those who were alert (RASS score of zero) at admission were included in the analysis. Descriptive analysis was used to show participant characteristics. The chi-square test was used to compare the proportions of variables between two groups with and without DHD; Fisher's exact test was used when the expected cell count was less than 5. The *t*-test was used to compare mean values of continuous variables. *P*-values were obtained from these tests. We used two-tailed

tests in each analysis, and a p -value less than 0.05 was considered as statistically significant. For cases with DHD, the proportions of the 12 reasons for DHD were calculated. A hierarchical cluster analysis using Ward's methods was conducted based on reasons for DHD. Cluster distance was determined using squared Euclidean distance. The number of clusters was determined by referring the results of scree plots and clinical interpretability of the characteristics of each cluster. To compare the statistical difference between each cluster pairs, multiple comparison was performed by using Fisher's exact test with Hochberg method for categorical variables and Tukey–Kramer test for continuous variables to adjust P -values. In addition, we explored a linear trend in proportions in patients with DHD and the wish for lethal drug administration according to the severity of depression using the Cochran–Armitage test. All statistical calculations were performed using IBM SPSS Statistics version 24 (IBM SPSS Inc., Armonk, NY, USA) and R version 3.6.1.

Results

A total of 1,633 of 1,896 participants died in PCUs during the study period. Of these, data from 971 patients with RASS scores of zero at admission were analyzed. Table 1 shows participant characteristics. The average age was 72 years [standard deviation (SD) = 12]. Common primary cancer sites were gastrointestinal tract (31%), liver/biliary ducts/pancreas (19%), and lung (15%). ECOG performance status was 3 or 4 for more than 80% of patients. The average survival time in the PCU was 31 days (SD = 33). Of 971 patients, 174 (18%: 95% CI, 16–20) had DHD. Of patients who had DHD, 79 (46%: 95% CI, 38–53) had an explicit wish for lethal drug administration. A comparison of characteristics between patients with or without DHD showed that PPS was significantly better in the group with DHD than in the group without DHD (44 vs. 42; $P < 0.01$). The duration of PCU stay was significantly longer in the group with DHD than in the group without DHD (40 days vs. 29 days; $P < 0.01$). The prevalence of any symptoms was not significantly different between the groups. Regarding preference and decision making, patients with DHD were more likely to choose PCU to avoid being a burden to others. Patients with DHD were more likely to be aware that they were dying, more likely to be involved with decision making and more prepared for their imminent death than patients without DHD.

Table 2 shows the proportion of each DHD reason. Dependency was the most frequent DHD reason (45%: 95% CI, 37–52), followed by burden to others (28%: 95% CI, 21–35), inability to engage in any pleasant activities (24%: 95% CI, 18–31) and meaninglessness/loss of value (24%: 95% CI, 18–31). Pain was significantly more frequent in patients who desired lethal drug administration than in those who did not.

We used a hierarchical cluster analysis to classify subgroups among patients with DHD. A dendrogram was created based on the patterns of DHD reasons. We referred the scree plots to determine the number of clusters (Supplementary Figure S1). Finally, five distinct clusters were obtained. Figure 1 shows the patterns of DHD reasons for the five clusters. Table 3 shows the characteristics of the five clusters. Patients in cluster 1 (“physical distress” 35%, 61/173) were more likely to have physical distresses such as dyspnea (38%), pain (23%), and other physical symptoms. The proportion of patients who expressed at least one physical symptoms as a reason for DHD was highest (70%) in cluster 1 among all clusters. Most patients (89%) in cluster 1 were using

opioid. Cluster 2 (“dependent and burdensome” 21%, 37/173) consisted of patients who expressed DHD owing to the distress of dependency (97%) and being a burden to others (51%). Patients in cluster 2 were more likely to have entered the PCU to avoid being a burden to others. Cluster 3 (“hopelessness” 19%, 33/173) was characterized by a high proportion of hopelessness (76%) and distress owing to the inability to engage in any pleasant activities (67%). They were more likely to be depressed and desire lethal drug administration (not statistically significant). In cluster 4 (“profound fatigue” 17%, 30/173), most patients had profound fatigue and were well prepared for death. Opioid dosage was lowest in this group. Cluster 5 (“extensive existential suffering” 7%, 12/173) consisted of patients who had wide range of distress including existential sufferings, hopelessness, and physical symptoms.

In addition, we explored a linear trend in proportions in patients with DHD and the wish for lethal drug administration according to the severity of depression using the Cochran–Armitage test (Supplementary Figure S2). There was a statistically significant linear trend in the proportion of patients with DHD and patients who desired lethal drug administration across ordered severity categories of depression ($P < 0.01$; $P < 0.01$, respectively).

Discussion

This study demonstrated five interpretable subgroups of terminally ill cancer patients with DHD. Many quantitative and qualitative studies have shown DHD-related factors in terminally ill cancer patients (Chochinov et al., 1995; Breitbart et al., 2000; McClain et al., 2003; Morita et al., 2004; O'Mahony et al., 2005; Mystakidou et al., 2006; Rodin et al., 2007; Villavicencio-Chávez et al., 2014; Wilson et al., 2016; Robinson et al., 2017; Vehling et al., 2017; Parpa et al., 2019). However, the use of cluster analysis is not common in palliative care research. The five clusters we found showed different characteristics.

About one-third of patients with DHD were in cluster 1 (physical distress). This group was characterized by a high proportion of physical distress, such as dyspnea and pain. Dyspnea and pain are reported as refractory symptoms in terminally ill cancer patients who eventually needed palliative sedation (Maltoni et al., 2012). Many patients in cluster 1 also had anxiety. Although the relationship between anxiety and pain is controversial, some reports indicate an association between physical distress and psychological distress (McMillan et al., 2008; Li et al., 2017; McKenzie et al., 2020). Additional research is needed to alleviate these refractory symptoms in terminally ill cancer patients.

Almost all patients in cluster 2 (dependent and burdensome) experienced distress related to dependency and more than half were distressed about being a burden to others. As cancer advances, patients lose their independence and need more help from others. Other studies have shown that feeling a burden to others is one of the main reasons for both DHD and requests for euthanasia in advanced cancer patients (Suarez-Almazor et al., 2002; Morita et al., 2004; Wilson et al., 2007; Akazawa et al., 2010). Indeed, 78% of cluster 2 patients chose to enter a PCU to avoid being a burden to their family. These cognitive and behavioral patterns may be common in terminally ill patients worldwide. Further research for the development of effective care for such existential distress is needed.

Cluster 3 (hopelessness) consisted of patients with hopelessness and distress related to the inability to engage in any pleasant activities. This is also consistent with the findings of previous

Table 1. Characteristics of participants with/without DHD

Demographics	No DHD (n = 797)		DHD (n = 174)		P
	n	%	n	%	
Age (years)					0.73
Mean (SD)	72	(13)	72	(11)	
Sex					0.77
Male	399	50	85	49	
Female	398	50	89	51	
Primary cancer site					0.84
Gastrointestinal tract	252	32	52	30	
Liver/biliary ducts/pancreas	150	19	33	19	
Lung	123	15	26	15	
Gynaecological	61	8	11	6	
Breast	56	7	11	6	
Urological	45	6	15	9	
Other	110	14	26	15	
ECOG performance status					0.19
1	6	1	3	2	
2	68	9	22	13	
3	429	54	92	53	
4	294	37	57	33	
PPS					<0.01
Mean (SD)	42	(11)	44	(12)	
Duration of PCU stay (days)					<0.01
Mean (SD)	29	(31)	40	(37)	
Marital status					0.1
Single	94	12	23	13	
Married	480	60	92	53	
Bereaved	173	22	40	23	
Divorced	49	6	19	11	
Lives with family					0.31
Yes	562	70	116	67	
No	235	30	58	33	
Religion					0.65
No specific religion	338	42	77	44	
Buddhism	84	11	17	10	
Christianity	17	2	3	2	
Shintoism	1	0	1	1	
Other	9	1	4	2	
Unknown	348	44	72	41	
Past psychiatric history					0.26
Yes	70	9	20	12	
No	727	91	154	88	
Current antipsychotic drug use					0.35
Yes	237	30	58	33	
No	560	70	116	67	

(Continued)

Table 1. (Continued.)

Demographics	No DHD (n = 797)		DHD (n = 174)		P
	n	%	n	%	
Abbreviated Mental Test score					<0.01
Normal cognition (≥ 4)	666	84	163	94	
Possible dementia (≤ 3)	131	16	11	6	
Pain ^a					0.43
Not at all, mild (IPOS 0, 1)	506	64	105	60	
Moderate, severe, overwhelming (IPOS 2, 3, 4)	290	36	69	40	
Dyspnea ^a					0.71
Not at all, mild (IPOS 0, 1)	641	81	138	79	
Moderate, severe, overwhelming (IPOS 2, 3, 4)	155	19	36	21	
Fatigue ^a					0.34
Not at all, mild (IPOS 0, 1)	466	59	95	55	
Moderate, severe, overwhelming (IPOS 2, 3, 4)	330	41	79	45	
Appetite loss ^a					0.40
Not at all, mild (IPOS 0, 1)	435	55	89	51	
Moderate, severe, overwhelming (IPOS 2, 3, 4)	361	45	85	49	
Peacefulness ^b					0.77
Always, most of time, sometimes	707	89	154	89	
Occasionally, not at all	85	11	20	11	
Depression ^c					0.08
Not at all, mild (IPOS 0, 1)	587	88	133	83	
Moderate, severe, overwhelming (IPOS 2, 3, 4)	47	7	20	12	
Impossible to assess owing to coma	33	5	8	5	
Anxiety ^c					0.1
Not at all, mild (IPOS 0, 1)	499	75	108	67	
Moderate, severe, overwhelming (IPOS 2, 3, 4)	135	20	45	28	
Impossible to assess owing to coma	33	5	8	5	
Physical distress during final days					0.40
Suffering	170	21	36	21	
Not at all, a little suffering	604	76	136	78	
Impossible to assess owing to coma	23	3	2	1	
Peacefulness during final days					0.09
Always, most of the time, sometimes	433	54	80	46	
Occasionally, not at all	255	32	70	40	
Impossible to assess owing to coma	109	14	24	14	
Preference and decision making					
Chose PCU to avoid being a burden to others					<0.01
Yes	351	44	101	58	
No	446	56	73	42	
Aware that he/she is dying					0.02
Completely aware, partially aware	711	89	169	97	
Unaware	29	4	4	2	

(Continued)

Table 1. (Continued.)

Demographics	No DHD (n = 797)		DHD (n = 174)		P
	n	%	n	%	
Unknown	57	7	1	1	
Acceptance of illness					0.07
Completely accepted, accepted	622	78	153	88	
Not accepted	63	8	11	6	
Unknown	112	14	10	6	
Shared decision making					<0.01
Neither patient nor family were involved	6	1	2	1	
Only family was involved	86	11	10	6	
Only patient was involved	39	5	23	13	
Both patient and family were involved	575	72	132	76	
Unknown	91	11	7	4	
Preparation for imminent death ^a					<0.01
Not prepared	72	9	9	5	
Only a family member was prepared	103	13	13	7	
Only the patient was prepared	49	6	17	10	
Both patient and family were prepared	455	57	118	68	
Unknown	117	15	17	10	

SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; PPS, palliative performance scale; IPOS, Integrated Palliative care Outcome Scale; PCU, palliative care unit; RASS, Richmond Agitation–Sedation Scale; DHD, desire for hastened death.

Data for 971 participants with RASS score of 0 at admission were included.

^aData for one participant in the group with no desire for death were missing.

^bData for five participants in the group with no desire for death were missing.

^cDepression and anxiety were assessed 1 week after admission for 828 patients.

empirical research to explore the reasons of request of PAS in the patients (McClain et al., 2003; Wilson et al., 2007). Hopelessness has been confirmed as a unique contributor to DHD that is distinct from depression (Breitbart et al., 1996; Chochinov et al., 1998). Our findings may support these previous evidences for an association between hopelessness and DHD among terminally ill cancer patients. The proportion of explicit wish for lethal drug in cluster 3 was highest. As shown in Supplementary Figure S2, wish for lethal drug may be associated with severe depression. The patients in this cluster may be at high risk of suicidal attempt. Further research is needed to identify how patients cope with their hopelessness and depression during the end phase of terminal illness.

Cluster 4 (profound fatigue) also showed unique characteristics. Most of the patients in this cluster had profound fatigue. On the other hand, they were well prepared for dying. Cancer-related fatigue is often induced by the progression of cachexia (Peixoto da Silva et al., 2020). For patients who are prepared for their own death, worsened cachexic symptoms could make them realize their imminent death. Expression of DHD from the patients in cluster 4 may represent their readiness for dying. Patients in cluster 5 (extensive existential suffering), smallest proportion among all clusters, were characterized by a wide range of distress. Further qualitative studies are needed to investigate how these distresses are interacting and how DHD is induced by these coexisting distresses.

The second important finding was that we identified the prevalence of the main reasons for DHD in terminally ill cancer patients. Similar to previous study findings, dependency and feeling a burden to others were the most common reasons for DHD (Wilson et al., 2007). Meaninglessness and loss of autonomy were also identified as major reasons for DHD. These findings are consistent with previous findings (McClain et al., 2003; Morita et al., 2004). Despite recent advances in pharmacotherapy, physical symptoms remain an important source of distress and a reason for DHD. These results highlight the importance of symptom management in cancer patients.

Study limitations

We should mention several limitations. First, all subjective data were assessed by the primarily responsible physicians. A total of 87 clinical physicians participated throughout the study period (an average of four physicians participated per site, and an average of 21 patients' data were retrieved by one physician). We acknowledge that this methodology may be related to low inter-rater reliability. However, the primarily responsible palliative physician, who obtained the presence/absence of DHD, evaluated patients almost every day and participated in daily interdisciplinary conference. Also, the principal investigator and lead investigators provided constant support for participating physicians during the study period to ensure accurate data collection. Such situations

Table 2. Reasons for desire for hastened death ($n = 173$)^a

Reasons ^b	All patients with desire for hastened death ($n = 173$)		No explicit wish for administration of lethal drug ($n = 94$)		Explicit wish for administration of lethal drug ($n = 79$)	
	<i>n</i>	% (95% CI)	<i>n</i>	%	<i>n</i>	%
Dependency	77	45 (37–52)	40	43	37	47
Burden to others	48	28 (21–35)	24	26	24	30
Inability to engage in any pleasant activities	42	24 (18–31)	20	21	22	28
Meaninglessness/loss of value	42	24 (18–31)	20	21	22	28
Profound fatigue	40	23 (17–30)	26	28	14	18
Dyspnea	37	21 (16–28)	23	24	14	18
Hopelessness	36	21 (15–28)	16	17	20	25
Loss of autonomy	31	18 (13–24)	17	18	14	18
Pain ^c	21	12 (7.7–18)	6	6.4	15	19
Other physical symptoms	17	10 (5.8–15)	6	6.4	11	14
Fear of death	15	8.7 (4.9–14)	5	5.3	10	13
Loneliness	6	3.5 (1.3–7.3)	3	3.2	3	3.8
No specific reasons	3	1.7 (0.36–5.0)	3	3.2	0	0.0

^aData were missing for 1 of 174 participants with a desire for death.

^bMultiple choices were allowed.

^cChi-square test showed a statistically significant difference between the two groups ($P < 0.05$).

and the acceptable concordance between physician-reported and family-reported prevalence of DHD may contribute to the reliability of data. Second, in this study, we did not use validated tools to assess DHD. The identification of DHD depended on the patient's expression. DHD is considered as a graded phenomenon, and validated scales exist to assess the severity of DHD (Chochinov et al., 1995; Rosenfeld et al., 1999; Wilson et al., 2016). The use of validated measures is important to improve

internal validity and to assess DHD that would never be expressed unless asked. Assessing patients' subjective distress without validated tools may have led to low data validity and reliability. However, responding to many questionnaires is often stressful for advanced cancer patients, and this may be linked with high attrition rates, especially in studies of palliative patients with deteriorating conditions (Chochinov et al., 1995; Breitbart et al., 2000; McClain et al., 2003). The participant inclusion criteria in this

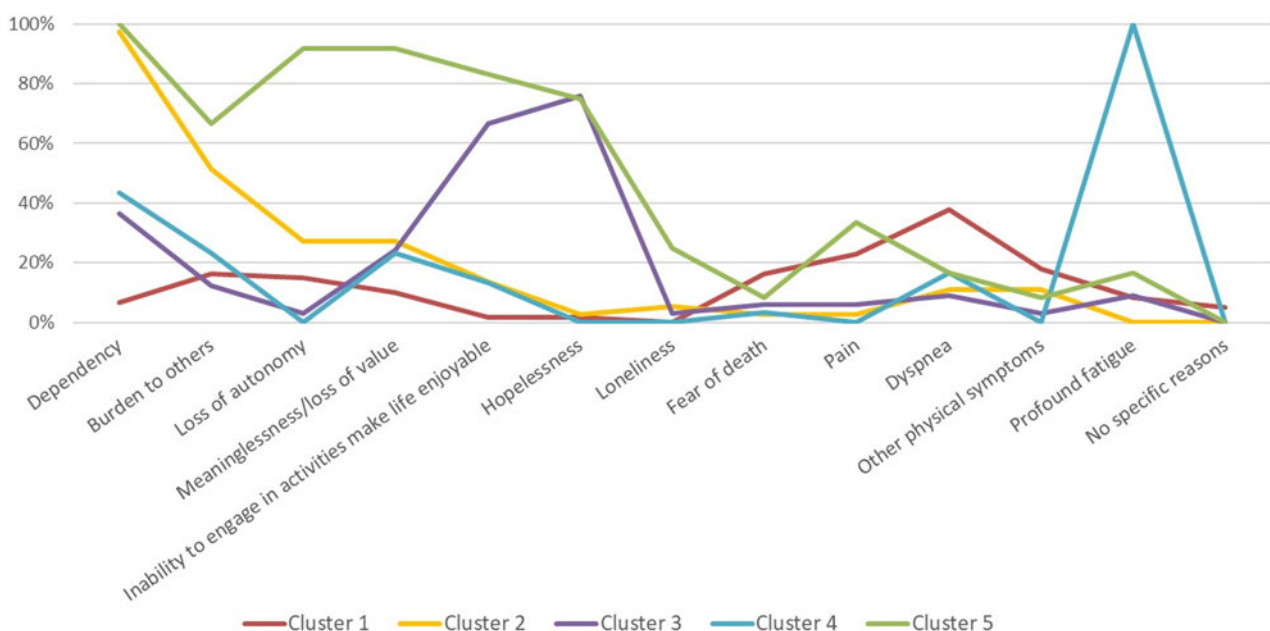
**Fig. 1.** Cluster analysis of reasons for desire for hastened death.

Table 3. Characteristics of five clusters of patients with desire for hastened death (n = 173)

	Cluster 1 (n = 61)		Cluster 2 (n = 37)		Cluster 3 (n = 33)		Cluster 4 (n = 30)		Cluster 5 (n = 12)		P ^a
	n	%	n	%	n	%	n	%	n	%	
Age											NS
Years (SD)	70	(11)	74	(9.9)	71	(9.3)	74	(11)	69	(16)	
Sex											NS
Male	29	(48)	15	(41)	19	(58)	15	(50)	7	(58)	
Primary cancer site											NS
Gastrointestinal tract	14	(23)	9	(24)	9	(27)	16	(53)	3	(25)	
Liver/biliary ducts/ pancreas	7	(11)	9	(24)	8	(24)	8	(27)	1	(4)	
Lung	13	(21)	7	(19)	2	(6)	1	(3)	3	(25)	
Gynaecological	8	(15)	1	(3)	1	(3)	0	(0)	1	(4)	
Breast	4	(7)	4	(11)	2	(6)	1	(3)	0	(0)	
Urological	6	(10)	3	(8)	3	(9)	3	(10)	0	(0)	
Other	9	(15)	4	(11)	8	(27)	1	(3)	4	(16)	
Marital status											NS
Single	6	(10)	5	(14)	7	(21)	3	(10)	2	(17)	
Married	33	(54)	15	(41)	16	(48)	20	(67)	8	(67)	
Bereaved	14	(23)	13	(35)	6	(18)	5	(17)	1	(8)	
Divorced	8	(13)	4	(11)	4	(12)	2	(7)	1	(8)	
Explicit wish for lethal drug											NS
Yes	29	(48)	18	(49)	19	(58)	8	(27)	5	(42)	
Reasons of DHD											
Physical symptoms ^b	43	(70)	9	(24)	6	(18)	0	(0)	4	(36)	c
Dependency	4	(7)	36	(97)	12	(36)	13	(43)	12	(100)	d
Burden to others	10	(16)	19	(51)	4	(12)	7	(23)	8	(67)	e
No activities that make life enjoyable	1	(2)	5	(14)	22	(67)	4	(13)	10	(83)	f
Hopelessness	1	(2)	1	(3)	25	(76)	0	(0)	9	(75)	f
Profound fatigue	5	(8)	0	(0)	3	(9)	30	(100)	2	(17)	g
Preparedness											
Patients and families were well prepared for dying (Yes)	36	(59)	20	(54)	23	(70)	29	(97)	9	(75)	h
Feeling of being a burden to others											
Chose PCU to avoid being a burden to others (Yes)	31	(51)	29	(78)	20	(61)	13	(43)	7	(58)	i
Depression ^j											NS
Moderate, severe, extreme (IPOS 2, 3, 4)	7/52	(13)	1/31	(3)	6/31	(19)	4/27	(15)	2/11	(18)	
Anxiety ^j											
Moderate, severe, extreme (IPOS 2, 3, 4)	23/52	(44)	4/31	(13)	7/31	(23)	7/27	(26)	4/11	(36)	k
Physical symptoms											NS
Physical condition in final days (severe, moderate)	16	(26)	5	(14)	8	(24)	5	(17)	2	(17)	

(Continued)

Table 3. (Continued.)

	Cluster 1 (n = 61)		Cluster 2 (n = 37)		Cluster 3 (n = 33)		Cluster 4 (n = 30)		Cluster 5 (n = 12)		P ^a
	n	%	n	%	n	%	n	%	n	%	
Opioid use											
Yes	54	(89)	21	(57)	21	(64)	15	(50)	8	(67)	l
MEDD, mg/day (SD)	83	(108)	101	(190)	61	(74)	46	(60)	164	(144)	
MEDD, median mg/day	40		24		30		24		105		
MEDD, minimum and maximum dose	5	444	10	672	5	336	6	240	23	400	
CDS											
Yes	17	(28)	7 ^m	(19)	1	(3)	8	(27)	2	(17)	n
CDS duration, mean days (SD) ^o	4.0	(4.8)	2.3	(2.5)	2.0	–	4.8	(3.9)	1.5	(0.7)	
Median ^o	3.0		0.5		2.0		2.8		1.5		
Physician feels uncomfortable with CDS initiation (Yes)	4/18	(22)	4/7	(57)	0	(0)	0	(0)	1/2	(50)	

SD, Standard Deviation; PCU, Palliative Care Unit; MEDD, Morphine Equivalent Daily Dosage; CDS, Continuous Deep Sedation; NS, No Significant Differences Between Any Groups; DHD, desire for hastened death.

^aMultiple comparisons were calculated by Fisher exact test with Hochberg Method and Tukey–Kramer test.

^bAt least one of pain, dyspnea, or other physical symptoms.

^cCluster 1 was significantly larger than cluster 2, 3, and 4; Cluster 4 was significantly smaller than clusters 2 and 5.

^dClusters 2 and 5 were significantly larger than clusters 1, 3, and 4; Cluster 1 was significantly smaller than clusters 3 and 4.

^eClusters 2 and 5 were significantly larger than clusters 1 and 3.

^fClusters 3 and 5 were significantly larger than clusters 1, 2, and 4.

^gCluster 4 was significantly larger than clusters 1, 2, 3, and 5.

^hCluster 4 was significantly larger than clusters 1 and 2.

ⁱCluster 2 was significantly larger than cluster 4.

^jDepression and anxiety assessed 1 week after admission; 152 participants were assessed.

^kCluster 1 was significantly larger than cluster 2.

^lCluster 1 was significantly larger than clusters 2 and 4.

^mCDS data is missing in cluster 2 (37 to >36) 7/16 = 19.4%.

ⁿCluster 1 was significantly larger than cluster 3.

^oThirty-six sets of data from patients who received CDS were analyzed.

study were not strict, and data were obtained prospectively from multiple centers across the country. These may help medical providers to apply the results of this study to the real-world clinical cases. Third, the robustness of the causal relationship between the variables measured and DHD was weak. The presence or absence of DHD was assessed at any time up to death. We did not record when DHD was assessed. There was more chance for physicians to identify expressions of DHD in patients with longer PCU stays (see Table 1: PPS and survival time were better for patients with DHD than for patients without DHD). A longitudinal study is needed to assess the causal relationships between DHD expression and potential DHD factors and outcomes. Fourth, the classification of patients with DHD was based on only the 12 reasons that we identified. Although we selected these categories carefully, there may be other factors not assessed here that are associated with DHD such as demoralization and entrapment (Gilbert and Allan, 1998; Robinson *et al.*, 2017; Vehling *et al.*, 2017). That might change the subgroup characteristics if added to the analysis.

Clinical implications

DHD in terminally ill cancer patients is a complex phenomenon and often involves multilayered distress. The clustering of terminally ill cancer patients with DHD into subgroups may be useful

for the assessment of their suffering. Further study is required to develop efficient care strategies for these patients.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S1478951521000080>.

Funding. This study was supported by a Grant-in-Aid from the Japan Hospice Palliative Care Foundation and was partially supported by JSPS KAKENHI Grant Number JP16KT0007.

Conflict of interest. The authors declare no conflict of interests.

References

- Akazawa T, Akechi T, Morita T, *et al.* (2010) Self-perceived burden in terminally ill cancer patients: A categorization of care strategies based on bereaved family members' perspectives. *Journal of Pain and Symptom Management* **40**, 224–234.
- Anderson F, Downing GM, Hill J, *et al.* (1996) Palliative performance scale (PPS): A new tool. *Journal of Palliative Care* **12**, 5–11.
- Balaguer A, Monforte-Royo C, Porta-Sales J, *et al.* (2016) An international consensus definition of the wish to hasten death and its related factors. *PLoS ONE* **11**, e0146184.
- Breitbart W, Rosenfeld BD and Passik SD (1996) Interest in physician-assisted suicide among ambulatory HIV-infected patients. *The American Journal of Psychiatry* **153**, 238–242. doi:10.1176/ajp.153.2.238

- Breitbart W, Rosenfeld B, Pessin H, *et al.* (2000) Depression, hopelessness, and desire for hastened death in terminally ill patients with cancer. *JAMA* **284**, 2907–2911.
- Chochinov HM, Wilson KG, Enns M, *et al.* (1995) Desire for death in the terminally ill. *The American Journal of Psychiatry* **152**, 1185–1191.
- Chochinov HM, Wilson KG, Enns M, *et al.* (1998) Depression, Hopelessness, and suicidal ideation in the terminally ill. *Psychosomatics* **39**, 366–370.
- Eisen MB, Spellman PT, Brown PO, *et al.* (1998) Cluster analysis and display of genome-wide expression patterns. *Proceedings of the National Academy of Sciences of the United States of America* **95**, 14863–14868.
- Ganzini L, Harvath TA, Jackson A, *et al.* (2002) Experiences of Oregon nurses and social workers with hospice patients who requested assistance with suicide. *New England Journal of Medicine* **347**, 582–588.
- Ganzini L, Goy ER and Dobscha SK (2008) Prevalence of depression and anxiety in patients requesting physicians' aid in dying: Cross sectional survey. *BMJ* **337**, a1682.
- Gilbert P and Allan S (1998) The role of defeat and entrapment (arrested flight) in depression: An exploration of an evolutionary view. *Psychological Medicine* **28**, 585–598.
- Gomes B, Higginson IJ, Calanzani N, *et al.* (2012) Preferences for place of death if faced with advanced cancer: A population survey in England, Flanders, Germany, Italy, the Netherlands, Portugal and Spain. *Annals of Oncology* **23**, 2006–2015.
- Hodkinson HM (1972) Evaluation of a mental test score for assessment of mental impairment in the elderly. *Age Ageing* **1**, 233–238.
- Imai K, Morita T, Mori M, *et al.* (2016) Development and linguistic validation of the Japanese version of the modified Richmond Agitation–Sedation Scale. *Palliative Care Research* **11**, 331–336 (in Japanese).
- Li XM, Xiao WH, Yang P, *et al.* (2017) Psychological distress and cancer pain: Results from a controlled cross-sectional survey in China. *Scientific Reports* **7**, 39397.
- Lochner C, Keuthen NJ, Curley EE, *et al.* (2019) Comorbidity in trichotillomania (hair-pulling disorder): A cluster analytical approach. *Brain and Behavior* **9**, e01456.
- Logan J, Hall J and Karch D (2011) Suicide categories by patterns of known risk factors: A latent class analysis. *Archives of General Psychiatry* **68**, 935–941.
- Maltoni M, Scarpi E, Rosati M, *et al.* (2012) Palliative sedation in end-of-life care and survival: A systematic review. *Journal of Clinical Oncology* **30**, 1378–1383.
- McClain CS, Rosenfeld B and Breitbart W (2003) Effect of spiritual well-being on end-of-life despair in terminally-ill cancer patients. *Lancet* **361**, 1603–1607.
- McKenzie E, Zhang L, Chan S, *et al.* (2020) Symptom correlates of dyspnea in advanced cancer patients using the Edmonton Symptom Assessment System. *Supportive Care in Cancer* **28**, 87–98.
- McMillan SC, Tofthagen C and Morgan MA (2008) Relationships among pain, sleep disturbances, and depressive symptoms in outpatients from a comprehensive cancer center. *Oncology Nursing Forum* **35**, 603–611.
- Morita T, Sakaguchi Y, Hirai K, *et al.* (2004) Desire for death and requests to hasten death of Japanese terminally ill cancer patients receiving specialized inpatient palliative care. *Journal of Pain and Symptom Management* **27**, 44–52.
- Mystakidou K, Parpa E, Katsouda E, *et al.* (2006) The role of physical and psychological symptoms in desire for death: A study of terminally ill cancer patients. *Psycho-Oncology* **15**, 355–360.
- Oken MM, Creech RH, Tormey DC, *et al.* (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology* **5**, 649–655.
- O'Mahony S, Goulet J, Kornblith A, *et al.* (2005) Desire for hastened death, cancer pain and depression: Report of a longitudinal observational study. *Journal of Pain and Symptom Management* **29**, 446–457.
- Parpa E, Tsilika E, Galanos A, *et al.* (2019) Depression as mediator and or moderator on the relationship between hopelessness and patients' desire for hastened death. *Supportive Care in Cancer* **27**, 4353–4358.
- Peixoto da Silva S, Santos JMO, Costa E Silva MP, *et al.* (2020) Cancer cachexia and its pathophysiology: Links with sarcopenia, anorexia and asthenia. *Journal of Cachexia, Sarcopenia and Muscle* **11**, 619–635.
- Robinson S, Kissane DW, Brooker J, *et al.* (2017) The relationship between poor quality of life and desire to hasten death: A multiple mediation model examining the contributions of depression, demoralization, loss of control, and low self-worth. *Journal of Pain and Symptom Management* **53**(2), 243–249.
- Rodin G, Zimmermann C, Rydall A, *et al.* (2007) The desire for hastened death in patients with metastatic cancer. *Journal of Pain and Symptom Management* **33**, 661–675.
- Rosenfeld B, Breitbart W, Stein K, *et al.* (1999) Measuring desire for death among patients with HIV/AIDS: The schedule of attitudes toward hastened death. *American Journal of Psychiatry* **156**, 94–100.
- Sakurai H, Miyashita M, Imai K, *et al.* (2019) Validation of the integrated palliative care outcome scale (IPOS) - Japanese version. *Japanese Journal of Clinical Oncology* **49**, 257–262.
- Suarez-Almazor ME, Newman C, Hanson J, *et al.* (2002) Attitudes of terminally ill cancer patients about euthanasia and assisted suicide: Predominance of psychosocial determinants and beliefs over symptom distress and subsequent survival. *Journal of Clinical Oncology* **20**, 2134–2141.
- Vehling S, Kissane DW, Lo C, *et al.* (2017) The association of demoralization with mental disorders and suicidal ideation in patients with cancer. *Cancer* **123**(17), 3394–3401.
- Villavicencio-Chávez C, Monforte-Royo C, Tomás-Sábado J, *et al.* (2014) Physical and psychological factors and the wish to hasten death in advanced cancer patients. *Psycho-Oncology* **23**, 1125–1132.
- Wilson KG, Chochinov HM, McPherson CJ, *et al.* (2007) Desire for euthanasia or physician-assisted suicide in palliative cancer care. *Health Psychology* **26**, 314–323.
- Wilson KG, Dalglish TL, Chochinov HM, *et al.* (2016) Mental disorders and the desire for death in patients receiving palliative care for cancer. *BMJ Supportive & Palliative Care* **6**, 170–177.
- Yao CA, Hu WY, Lai YF, *et al.* (2007) Does dying at home influence the good death of terminal cancer patients? *Journal of Pain and Symptom Management* **34**, 497–504.