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Prevalence and associated factors of orphan symptoms in advanced cancer patients: a multicenter observational study

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Abstract (230words)

Purpose. The aim of this study was to examine the prevalence of myoclonus, sweating, pruritus, hiccup, vesical and rectal tenesmus, and to explore associated factors in patients with advanced cancer.

Methods. This multicenter prospective cohort study was conducted in 23 inpatient hospices/palliative care units in Japan from January to December 2017. The prevalence and characteristics of each symptom were assessed on admission and in the three days before death. We selected factors that might influence the occurrence of each symptom and investigated the association.

Results. A total of 1896 patients were enrolled. The prevalence of orphan symptoms rose from admission to the three days before death: myoclonus 1.3% to 5.3% (95%CI 0.9-1.9%/4.3-6.5%), sweating 1.8% to 4.1% (95%CI 1.3-2.6%/3.1-5.1%), hiccup 1.1% to 1.8% (95%CI 0.7-1.7%/1.2-2.6%), and tenesmus 0.7% to 0.9% (0.4-1.2%/0.5-1.5%). Prevalence of pruritus fell from 3.5% to 2.5% (95%CI 2.7-4.4%/1.8-3.4%). Sweating, pruritus, and hiccups persisted throughout the day in nearly half of the patients. Myoclonus was significantly associated with brain tumors, sweating with opioids and antipsychotics, pruritus with liver and biliary tract cancer, cholestasis and severe diabetes, hiccup with male gender, digestive tract obstruction, severe diabetes and renal failure. Vesical tenesmus was associated with urinary cancer, antipsychotics, and anticholinergics and rectal tenesmus with pelvic cavity cancer.

Conclusion. We found that orphan symptoms occurred in 0.5-5.0% of patients, increased over time except for pruritus, and persisted in half of the patients.

Keywords

Palliative care, myoclonus, sweating, pruritus, hiccup, tenesmus

Running title

Orphan symptoms in advanced cancer patients

Declarations

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Consent to participate: Opt-out methods were employed and written informed consent was waived according to the Japanese Ethical Guidelines for Epidemiology Research and guidance of institutional review boards.

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Authors' contributions:

Kaoru Nishijima: Conceptualization, Formal Analysis, Writing-Original Draft

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Introduction

Symptom management is an essential part of palliative care and important to achieve optimal quality of life. Advanced cancer patients have a variety of distressing symptoms, which are generally exacerbated close to death. However, some symptoms can be alleviated if appropriate palliative treatment is applied. [1, 2] Routine symptom assessment represents the cornerstone of symptom management. Validated symptom assessment tools such as the Edmonton Symptom Assessment System (ESAS) and the Integrated Palliative care Outcome Scale (IPOS) are widely used and contribute to screening physical and mental symptoms and measuring palliative care outcome. [3, 4] However, some symptoms, such as myoclonus, sweating, pruritus, hiccup and tenesmus, are rarely evaluated in most symptom assessment tools and can be considered orphan symptoms. Yet, they sometimes cause severe distress. [5-8] A systematic review investigating the frequency of symptoms in patients with incurable cancer reported that the prevalence of pruritus was 10% (95% CI 7-15%) and of hiccup 7% (95% CI 3-15%). [9] In a study investigating opioid-induced neurotoxicity, the frequency of opioid-induced myoclonus was 5.4 -17%. [10, 11] Sweating has been registered in 16-28% of cancer patients. [12, 13] Also, the reported prevalence of rectal tenesmus in patients with recurrent rectal carcinoma is around 14% .[14] In home palliative care settings, myoclonus occurred in 0.3%, sweating in 5%, pruritus and hiccups equally in 4%, and tenesmus in 2% of patients with advanced cancer. [6] However, the results of these studies cannot be generalized to patients with advanced cancer in inpatient hospices or palliative care units due to differences in study settings and study population, particularly the prevalence of myoclonus and tenesmus in terminally ill cancer patients, which is still unknown. Previous studies included small numbers of patients or assessed specific populations (e.g. patients using opioids). Furthermore, to our best knowledge, the pre-mortem prevalence of these symptoms, except for myoclonus, has not been reported.

The primary aim of the present study was to identify the prevalence of myoclonus, sweating, pruritus, hiccup and tenesmus in patients with advanced cancer who were admitted to inpatient hospices and palliative care units. We also compared the prevalence of each orphan symptom on admission and in the three days before death to elucidate the continuity of these symptoms. In addition, we explored the characteristics of each orphan symptom and associated factors.

Methods

This multicenter prospective cohort study was performed at 23 inpatient hospices and palliative care units in Japan from January to December 2017. We recorded patient background data, symptoms and clinical treatment. The attending physician or nurse in charge of each patient recorded all outcome measures on the day of admission and followed up all patients until death or discharge. Although patient-reported outcomes are the gold standard for assessing the prevalence and severity of the symptoms, they are difficult to collect from patients just before death because of impaired consciousness or high symptom burden. In order to avoid missing data and to use the same method of investigation at the time of admission and just before death, we decided to use the health care providers' records for assessing symptoms.

The study was conducted in compliance with the Declaration of Helsinki and the ethical guidelines for epidemiological research presented by the Ministry of Health, Labor and Welfare in Japan. Written informed consent was waived but we disclosed information to guarantee the opportunity for patients to refuse. The ethics review boards of each participating institution approved the protocol.

Subjects

Eligible patients were consecutively enrolled in the study if they had been newly admitted to

palliative care units during the study period. Inclusion criteria were age ≥ 18 years, a diagnosis of locally extensive or metastatic cancer, and admission to palliative care units. Patients were excluded if they were scheduled to be discharged or transferred within a week, or expressed intention to refuse to participate in this study.

Procedure

Data were collected on the day of admission and on the day of death. The latter were recorded recalling the last three days before death. The primary responsible palliative care physician recorded the presence or absence and characteristics of orphan symptoms according to the following definitions by observing and/or asking the patient.

Definition

Before starting this study, the research group defined each symptom based on a literature review [6,15,16,17,18-20] and discussions among researchers.

Myoclonus was defined as a brief, involuntary twitching of a muscle or a group of muscles. Severity was assessed using the Unified Myoclonus Rating Scale (0=absent, 1=once every 10 seconds, 2=two or three times every 10 seconds, 3=four to nine times every 10 seconds, 4=ten times or more every 10 seconds). [15] Sweating was defined as drenching sweats that require the patient to change bedclothes. [16] Characteristics were categorized as nocturnal or persistent, i.e. symptoms that last all day. [6] Pruritus was the symptomatic level or quality of itch that was defined as an intense cutaneous discomfort occurring with pathological changes in the skin or body and eliciting vigorous scratching. [17] Characteristics were categorized as intermittent or persistent. [6] Hiccup was defined as an involuntary contraction of the muscles of inspiration causing a sudden sharp inspiration and closure of the glottis that results the “hic” sound. [18] Severity was categorized as bout, protracted (more than 48 hours, less than one month) or continuous (more than one month). [18-20] Tenesmus was defined as a sensation of fullness or incomplete relief during urination or defecation. [14,21]

Measurement

The primary outcome measure was prevalence of myoclonus, sweating, pruritus, hiccup and vesical/rectal tenesmus on admission. The primary responsible palliative care physician confirmed the presence or absence of each symptom through interviews and/or physical examination. They consulted patients directly at least three times a day, and as such, their observations can proxy for patient-reported outcomes to some extent. We also investigated the prevalence of the same orphan symptoms in the last three days before death. At the time of the patient's death, the physician recalled these symptoms in the three days before death.

Secondary outcomes were the severity and characteristics of each symptom and the factors associated with each symptom. We collected demographic data and clinical characteristics of the study participants, including age, sex, site of primary cancer and metastatic disease, comorbidities and indicators of general conditions (according to Eastern Cooperative Oncology Group Performance Status and Karnofsky's Performance Status) on admission. Comorbidity was diagnosed by palliative care physicians at each facility based on the Charlson Comorbidity Index. Relevant laboratory findings were recorded if tests were performed between one week before and three days after admission.

The potential associated factors for each of the orphan symptoms were determined based on a literature review [6,14,16-18,22] and discussions among authors. The following items were determined as potentially relevant factors: 1) myoclonus: primary or metastatic brain tumor, cerebrovascular disease, liver failure (cirrhosis with portal hypertension), renal failure (Cre ≥ 3 mg/dl), diabetes with any of the three major complications, fever ($\geq 37.5^{\circ}$ C), opioids (use and dosage), antipsychotics, benzodiazepine, antidepressants, anticholinergics; 2) sweating: primary or metastatic brain tumor, hematological malignancy, cerebrovascular disease, liver failure, renal failure, diabetes with any of the three major complications, fever, opioids, antipsychotics, benzodiazepine, antidepressants, anticholinergics; 3) pruritus:

primary or metastatic brain tumor, primary or metastatic liver tumor, bile duct or gall bladder tumor, pancreatic tumor, hematological malignancy, liver failure, renal failure, diabetes with any of the three major complications, complication of skin lesions, complication of cholestasis (defined as total bilirubin ≥ 10.0 mg/dl), opioids, antipsychotics, benzodiazepine, antidepressant, anticholinergics; 4) hiccups: primary or metastatic brain tumor, primary or metastatic liver tumor, esophageal tumor, stomach tumor, bile duct or gall bladder tumor, pancreatic tumor, cerebrovascular disease, liver failure, renal failure, diabetes with any of the three major complications, complication of digestive tract obstruction, opioids, antipsychotics, benzodiazepine, antidepressants, anticholinergics; 5) vesical and rectal tenesmus: gynecological tumor, urinary tumor, rectal tumor, pelvic cavity (gynecological + urinary + rectal) tumor, cerebrovascular disease, liver failure, renal failure, diabetes with any of the three major complications, fever, opioids, antipsychotics, benzodiazepine, antidepressants, anticholinergics. Information on each of these items was examined at the time of admission. Additionally, in the assessment at the time of death, if the responsible physician judged that drug-induced sweating was suspected, we asked them to choose the suspected drug from 1) opioids, 2) antidepressants, 3) nonsteroidal anti-inflammatory drugs, 4) acetaminophen, 5) acyclovir, all of which have been reported as drugs causing sweats [16], or to otherwise report the name of the drug. Similarly, we required a written report from the physician if they could suggest a cause for a patient's pruritus.

Statistical analysis

We performed descriptive statistics and calculated 95% confidence intervals (95% CI) for the prevalence and characteristics of orphan symptoms, patient demographics, comorbidities, concurrent drugs, and laboratory findings. Median days of survival and 95% CI for patients discharged due to death were calculated by the Kaplan-Meier method. We calculated odds ratios of each symptom corresponding to patient background characteristics, i.e., age, gender,

tumor sites, comorbidities, complications and medications. Complications investigated were: fever, malignant bowel obstruction, cholestasis (defined as total bilirubin $\geq 10\text{mg/dL}$), and skin lesion. We examined only variables that were pathophysiologically relevant for the development of the symptom. Multivariate analyses were not performed because of the low symptom prevalence. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a modified version of R (The R Foundation for Statistical Computing, Vienna, Austria). [23] Statistical significance was assumed if $P < 0.05$.

Results

A total of 1971 patients were initially enrolled. Of those, we excluded patients who were scheduled to be discharged within a week (42 patients) or declined to participate in this study (three patients), and data of 30 patients were lost. The remaining 1896 patients were analyzed. The prevalence of symptoms in the three days before death was analyzed for 1633 patients who died in a palliative care unit.

Baseline characteristics of the study subjects are summarized in Table 1. Median age of the patients was 74 years. Digestive organs were the most frequent site of primary cancer followed by cancer of the pancreas/liver/bile duct/gall bladder. Of all patients, 51.6% had a Karnofsky's Performance Scale of 30 or 40 on admission, 49% had Eastern Cooperative Oncology Group Performance Status 4, and the median survival of patients who died in palliative care was 19 days (95%CI 18-20 days).

The prevalence of each orphan symptom on admission and in the three days before death are reported in Table 2. The prevalence of myoclonus rose from 1.3% to 5.3% between the day of admission and the last three days of life, sweating rose from 1.8% to 4.1%, hiccup from 1.1% to 1.8%, and tenesmus from 0.7% to 0.9%. The prevalence of pruritus fell from

3.5% to 2.5%,

The characteristics of each orphan symptom on admission and in the three days before death are reported in Table 3. Forty per cent of patients complained of sweating, 39% with pruritus, and 62% with hiccups exhibited persistent symptoms. In tenesmus, rectal tenesmus was observed in three cases and vesical tenesmus in six cases. Two of 13 cases complained of a combined form of both vesical tenesmus and rectal tenesmus at the time of admission and 7/15 (47%) just before death.

Table 4 shows the results of a univariate analysis of the factors associated with each symptom. Myoclonus was significantly associated with brain tumors as a primary and metastatic site of cancer. Sweating was associated with opioid use ($P=0.00994$), especially morphine ($P=0.00245$). Pruritus was associated with cholestasis ($P=0.000000925$). Significant differences were also found in other factors that may cause cholestasis such as liver tumors as a primary and metastatic site of cancer ($P=0.00122$), bile duct and gall bladder cancer ($P=0.00526$). Pruritus was also strongly associated with diabetes with any of the three major complications ($P=0.00059$). Hiccups were associated with gastrointestinal obstruction ($P=0.00222$), diabetes with any of the three major complications ($P=0.00158$), male gender ($P=0.00271$) and renal failure ($P=0.0116$). Vesical tenesmus was associated with urinary tract tumor, use of antipsychotics and anticholinergics, whereas rectal tenesmus was associated with pelvic cavity tumors as a primary site of cancer. In the opinion of the attending physician, opioids were the most likely drug causing sweating ($n=14/66$), while cholestasis was considered the main probable cause of pruritus ($n=8/41$).

Discussion

To the best of our knowledge, this is one of the largest prospective multicenter studies to elucidate the prevalence and characteristics of orphan symptoms in patients with advanced

cancer who were admitted to inpatient hospices and palliative care units. The most important finding of this study was the prevalence of myoclonus, sweating, pruritus, hiccups and tenesmus on admission. In this study, the prevalence of each symptom was 0.5-5.0%. This prevalence was roughly consistent with a previous study that reported 0.3-5.0% in 362 patients with advanced cancer referred to home hospice care [6]. In contrast, the prevalence of some symptoms was lower than reported in other studies, such as sweating 16% [13], pruritus 10% [9], and hiccups 7% [9]. We conclude these differences are due to variance in patient background, primary site of cancer, treatment stage and prognosis of the study patients.

The second important objective of our study was to determine possible factors associated with the prevalence of each orphan symptom. Sweating is controlled by a center in the preoptic and anterior regions of the hypothalamus where thermosensitive neurons are located and may be influenced by various factors, such as infection, hormonal withdrawal, endocrine disorders, lymphoma, carcinoid syndrome and drugs including withdrawal [6, 16, 24]. In our study, sweating was associated with opioid use, especially morphine. From the point of view of the attending physician, opioids were the most frequent drugs to cause sweating. A few case reports have noted sweating while using opioids, and have suggested anticholinergic drugs as effective treatments. [25-27] Future research is needed on the effective treatment of sweating caused by opioids.

Pruritus may be the result of a dermatological or non-dermatological disease. Especially in non-diseased skin, it may be caused by systemic (e.g. cholestasis, chronic renal failure, metabolic and endocrine disease, hematologic disorder), neurological or psychiatric diseases as well as adverse effects of medication. [17, 28]. In the present study, pruritus was highly associated with cholestasis. From the point of view of the attending physician, cholestasis was also the most suspected cause of pruritus. Significant differences were also

found in other factors that may cause cholestasis such as liver cancer, bile duct and gall bladder cancer. There are several helpful reviews regarding the treatment of cholestasis associated pruritus [29-32]. In contrast, there was no positive association with opioid use and pruritus in this study. Pruritus is one of the most common adverse effects of opioids, and the risk significantly increases when opioids are given epidurally or intrathecally [33]. Also, in most cases, higher doses of opioids correlate with a higher incidence of pruritus [34]. Few patients in this study received neuraxial opioids and a lower dose of opioid (median of oral morphine equivalent daily dose = 30mg) may be the reason why we detected no association with pruritus.

Hiccups are caused by stimulation or damage to the vagus nerve, the phrenic nerve, or the brainstem, i.e. hiccup center. [18-21]. The pathogenesis of hiccups varies due to the length of the nerve reflex pathway, and the most common etiologies of persistent and intractable hiccups are pathologies of the gastrointestinal tract, of the thoracic and peritoneal viscera, and of the central nervous system [21]. Our results confirmed the association with digestive tract obstruction, diabetes with any of the three major complications, male gender and renal failure. These findings were consistent with previous studies [6, 35, 36]. Diabetes with any of the three major complications was also strongly associated with pruritus. These results suggest that comorbid diabetes may be a cause of symptoms in patients with advanced cancer in hospice or palliative care units.

The third important finding of this study related to changes in symptom prevalence on admission and in the three days before death in inpatient hospices and palliative care units. The prevalence of pruritus in the three days before death was lower than at the time of admission. This is the first report on this aspect as far as we know. There are two possible interpretations of why the frequency of pruritus decreased just before death. The first interpretation is that treatment may have been sufficient to improve the pruritus. Another

interpretation is that since itching is a more subjective symptom, the patient would be no longer able to complain about the symptom due to possibly reduced consciousness just before death. In contrast to this finding, the prevalence of myoclonus, sweating, hiccups, and bladder and rectal tenesmus were increased in the three days before death compared to on admission, despite receiving palliative care. These findings are consistent with previous studies reporting that myoclonus was more frequent in patients nearing death and night sweat was one of the most difficult symptoms to alleviate, and worsened in the last 48 hours [10.11.37, 38]

The fourth important finding of this study pertains to the severity and characteristics of each orphan symptom. When assessing the severity of symptoms, patient-reported outcomes are the gold standard. However, because patient-reported outcomes could not be assessed in this study due to the study design, the severity of the symptoms was assumed to be more distressing if the symptoms were persistent rather than paroxysmal or intermittent. These findings suggest that orphan symptoms may be burdensome although the prevalence is relatively low.

This study had several limitations. First, our study is based on a physician's report of the symptoms, not patient-reported outcome in most cases. Although this is standard practice in observational studies, these orphan symptoms are rarely subject to comprehensive standardized symptom assessments such as the ESAS, and may have been underestimated. Especially pruritus as a more subjective symptom, patients may not have been able to voice their complaints in the last days of life. Second, there may be recall bias to collect the data on the symptoms in the three days before death because of the study design. Third, we did not follow up on patients who were discharged alive from palliative care units. Their reports of pre-mortem symptoms may affect the outcome of pre-mortem symptom prevalence. However, we believe that the number is small and has little effect on the results. Fourth, multiple logistic regression analysis could not be performed to determine factors associated

with the prevalence of each orphan symptom due to insufficient sample size owing to the lower prevalence. Fifth, the use of corticosteroids was not included in the independent variable of hiccup. Previous studies have shown that corticosteroids, especially dexamethasone, cause hiccups. [39-45] However, many of these studies are on patients undergoing chemotherapy. It is worthwhile for further research to investigate whether steroid use contributes to hiccups in terminally ill cancer patients.

In conclusion, in this larger prospective study, we identified the prevalence of orphan symptoms in patients with advanced cancer in hospice and palliative care units. These symptoms may reduce the quality of life when insufficient symptomatic relief is provided, even with specialist palliative care. We believe understanding the underlying pathophysiology of each symptom stemming from the combination of tumor sites, comorbidities, and medications can lead to appropriate symptom relief. Larger studies are needed to determine the causes of each symptom and to confirm the effectiveness of empirical treatments.

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Table 1: Demographics and clinical characteristics of 1896 study patients.

Characteristics	No. or	% or
	Median	Range
Age, years (median, range)	74	25-100
Sex		
Men	965	50.9
Women	931	49.1
Site of primary cancer		
Esophagus, stomach, small intestine, colon, and rectum	519	27.4
Pancreas, liver, bile duct, gall bladder	363	19.1
Lung	319	16.8
Breast	131	6.9
Ovary, uterus	119	6.3
Kidney, urinary tract, bladder	101	5.3
Head and neck	76	4.0
Hematological	56	3.0
Prostate	40	2.1
Unknown	35	1.8
Brain	30	1.6
Bone, Soft tissue	21	1.1

Others	86	4.5
Site of metastasis		
Anywhere	1605	84.7
Liver	730	38.5
Lung	708	37.3
Bone	501	26.4
Brain	263	13.9
Comorbidity		
Cerebral vascular disease	127	6.7
Diabetes with any of the three major complications	43	2.3
Liver failure (Cirrhosis with portal hypertension)	48	2.5
Renal failure (Cre ≥ 3 mg/dl)	30	1.6
Karnofsky Performance Scale		
≥ 50	572	30.2
30-40	979	51.6
10-20	345	18.2
ECOG Performance Status		
0-1	26	1.4
2	156	8.2
3	785	41.4
4	929	49.0

Body temperature (°C, median, range, n=1864)	36.8	34.6-40.9
Chemotherapy in the previous month	172	9.1
Digestive tract obstruction	257	13.6
Concurrent medical interventions		
Opioids	1206	63.6
Oral morphine equivalent daily dose (mg, median, range, n=1201)	30	0.5-1200
Antipsychotics	429	22.6
Benzodiazepine	324	17.1
Antidepressant	77	4.1
Anticholinergics	69	3.6
Anticonvulsants	35	1.8
Laboratory (median, range)		
Total bilirubin (mg/dl, n=1577)	0.6	0-40.8
C-reactive protein (mg/dl, n=1581)	5.15	0-42.45
Serum sodium (mEq/l, n=1617)	136	101-187
Serum potassium (mEq/l, n=1614)	4.4	2.1-8.0
Corrected calcium (mg/dl, n=1403)	8.5	4.0-17.4
Survival of patients discharged due to death (median days, 95%CI, n=1633)	19	18-20

Table 2: Prevalence of each orphan symptom on admission and in the three days before death

On admission (n=1896)				In the three days before death (n=1633)		
Symptom	n	Prevalence (%)	95% CI ¹ (%)	n	Prevalence (%)	95% CI ¹ (%)
Myoclonus	25	1.3	0.9-1.9	87	5.3	4.3-6.5
Sweating	35	1.8	1.3-2.6	66	4.1	3.1-5.1
Pruritus	66	3.5	2.7-4.4	41	2.5	1.8-3.4
Hiccup	21	1.1	0.7-1.7	30	1.8	1.2-2.6
Tenesmus	13	0.7	0.4-1.2	15	0.9	0.5-1.5

¹ Confidence interval

Table 3: Characteristics of each orphan symptom on admission and in the three days before death

Symptom	On admission (n=1896)			In the three days before death (n=1633)		
	n	Ratio ¹ (%)	95% CI ² (%)	n	Ratio ¹ (%)	95% CI ² (%)
Myoclonus	25			87		
once/10 sec	14	56	35 - 76	58	67	56 - 76
2-3 times/10 sec	9	36	18 - 58	19	22	14 - 32
4-9 times/10 sec	2	8	1 - 26	8	9	4 - 17
≥ 10 times/10 sec	0			2	2	0.3 - 8
Sweating	35			66		
Nocturnal	21	60	42 - 76	30	46	33 - 58
Persistent	14	40	24 - 58	36	55	42 - 67
Pruritus	66			41		
Intermittent	40	61	48 - 72	23	56	40 - 72
Persistent	26	39	28 - 52	18	44	29 - 60

Hiccup	21			30		
Occasional	8	38	18 - 62	16	53	34 - 72
Protracted						
(≥ 48 hours, <1 month)	13	62	38 - 82	13	43	26 - 63
Continuous						
(≥ 1 month)	0			1	3	0.1 - 17
Tenesmus	13			15		
Rectal	3			3		
Vesical	8			5		
Both	2	15	2 - 45	7	47	21 - 73

¹ Proportion of each characteristic in each symptom

² Confidence interval

Table 4: Factors associated with orphan symptoms

	Myoclonus (n=25)				Sweating (n=35)		
	N	Odds ratio	95%CI	P value	Odds ratio	95%CI	P value
Sex (male)	965	1.45	0.61-3.64	0.42	1.46	0.74-2.88	0.28
Age (≥ 75)	901	0.73	0.29-1.76	0.55	0.65	0.3-1.35	0.24
Tumor site							
Brain (primary or/and metastasis)	286	2.69	1.15-6.30	0.0222*	1.17	0.48-2.84	0.73
Hematological	56	N/A ¹	N/A ¹	N/A ¹	0.97	0.13-7.18	0.97
Comorbidity							
Cerebral vascular disease	127	1.21	0.28-5.21	0.79	1.31	0.4-4.35	0.66
Liver failure (Cirrhosis with portal hypertension)	48	0	0-6.26	1	2.39	0.56-10.3	0.24
Renal failure (Cre ≥ 3 mg/dL)	30	2.65	0.35-20.2	0.35	1.86	0.25-14.0	0.55
Diabetes with any of the three major complications	43	1.81	0.24-13.7	0.56	2.69	0.62-11.6	0.18
Complication							
Fever ($\geq 37.5^{\circ}$ C)	901	2.05	0.59-5.7	0.19	0.76	0.23-2.49	0.64
Medication							
Opioids	1206	1.82	0.73-4.59	0.2	3.49	1.35-9.05	0.00994*
Opioid morphine-equivalent daily dose ≥ 120 mg	220	2.35	0.80-6.94	0.12	2.58	1.05-6.31	0.0385*
Morphine	363	1.06	0.39-2.83	0.91	2.89	1.45-5.74	0.00245*
Antipsychotics	429	1.54	0.66-3.59	0.32	2.2	1.11-4.37	0.0237*
Benzodiazepine	324	0.92	0.32-2.71	0.88	0.81	0.31-2.09	0.66
Antidepressant	77	0.98	0.13-7.37	0.99	1.44	0.34-6.12	0.62
Anticholinergics	69	1.1	0.15-8.28	0.92	0	0-2.96	0.64

	Pruritus (n=66)				Hiccups (n=21)		
	N	Odds ratio	95%CI	P value	Odds ratio	95%CI	P value
Sex (male)	965	1.61	0.97-2.67	0.07	9.33	2.17-40.1	0.00271*
Age (≥ 75)	901	0.999	0.98-1.02	0.92	0.99	0.95-1.02	0.36
Tumor site							
Brain (primary or/and metastasis)	286	0.66	0.30-1.46	0.3	0.28	0.04-2.09	0.21
Esophagus	62	N/A ¹	N/A ¹	N/A ¹	1.49	0.2-11.3	0.70
Stomach	203	N/A ¹	N/A ¹	N/A ¹	2.65	0.96-7.3	0.06
Liver (primary or/and metastasis)	775	2.29	1.39-3.79	0.00122*	2.37	0.98-5.75	0.0557
Bile duct,Gall bladder	72	3.22	1.42-7.33	0.00526*	1.27	0.17-9.60	0.82
Pancreas	202	0.84	0.36-1.95	0.68	2.66	0.97-7.34	0.0587
Hematological	56	1.03	0.25-4.31	0.97	N/A ¹	N/A ¹	N/A ¹
Comorbidity							
Cerebral vascular disease	127	1.15	0.45-2.91	0.77	1.47	0.34-6.40	0.61
Liver failure (Cirrhosis with portal hypertension)	48	2.62	0.91-7.52	0.07	1.94	0.26-14.8	0.52
Renal failure (Cre ≥ 3 mg/dL)	30	2.01	0.50-8.63	0.34	6.94	1.54-31.2	0.0116*
Diabetes with any of the three major complications	43	4.85	1.97-11.9	0.00059*	7.65	2.16-27.0	0.00158*
Complication							
Skin lesions	156	1.57	0.74-3.35	0.25	N/A ¹	N/A ¹	N/A ¹
Cholestasis (T-Bil>10.0mg/dl)	65	7.84	3.88-15.80	0.00000000925*	N/A ¹	N/A ¹	N/A ¹
Digestive tract obstruction	257	N/A ¹	N/A ¹	N/A ¹	4.02	1.65-9.79	0.00222*
Medication							
Opioids	1206	0.876	0.53-1.45	0.61	0.63	0.26-1.48	0.29
Opioid morphine-equivalent daily dose ≥ 120 mg	220	0.569	0.18-1.83	0.34	0.6	0.08-4.53	0.62
Morphine	363	1.14	0.63- 2.09	0.66	0.44	0.05-1.84	0.4
Antipsychotics	429	1.43	0.84-2.45	0.19	1.02	0.37-2.79	1
Benzodiazepine	324	1.2	0.65-2.22	0.57	1.14	0.38-3.42	0.81
Antidepressant	77	0.73	0.18-3.04	0.67	0	0-4.58	1
Anticholinergics	69	1.27	0.40-4.16	0.69	0	0-5.15	1

	Vesical tenesmus (n=10)				Rectal tenesmus (n=5)		
	n	Odds ratio	95%CI	P value	Odds ratio	95%CI	P value
Sex(Male)	965	2.26	0.58-8.77	0.24	1.45	0.24-8.69	0.69
Age(≥ 75)	901	1.03	0.97-1.08	0.38	0.955	0.90-1.02	0.14
Tumor site							
Gynecological	119	0	0-6.71	1	3.76	0.42-33.9	0.24
Urinary	141	5.43	1.39-21.2	0.0151*	3.13	0.35-28.1	0.31
Rectal	88	0	0-9.27	1	5.18	0.57-46.9	0.14
Pelvic cavity (gynecological + urinary + rectal)	348	1.91	0.49-7.44	0.35	6.72	1.12-40.4	0.0373*
Comorbidity							
Cerebral vascular disease	127	3.52	0.74-16.8	0.11	3.5	0.39-31.6	0.06
Liver failure (Cirrhosis with portal hypertension)	48	0	0-17.6	1	0	0-43.0	1
Renal failure (Cre ≥ 3 mg/dL)	30	0	0-29.0	1	0	0-70.2	1
Diabetes with any of the three major complications	43	0	0-19.8	1	0	0-48.2	1
Complication							
Fever ($\geq 37.5^\circ \text{C}$)	901	1.1	0.25-4.82	1	5.43	0.45-47.7	0.1
Medication							
Opioids	1206	1.34	0.35-5.19	0.68	0.858	0.14-5.15	0.87
Antipsychotics	429	4.93	1.38-17.5	0.0138*	2.17	0.36-13.0	0.4
Benzodiazepine	324	3.26	0.92-11.6	0.07	3.25	0.54-19.5	0.2
Antidepressant	77	0	0-10.7	1	0	0-26.1	1
Anticholinergics	69	6.78	1.41-32.6	0.0167*	6.7	0.74-60.7	0.09

*not applicable: Factors not associated with symptoms were not included in the formula