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Risk factors of sudden unexpected death in patients with advanced cancer near the end of life

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Original Article

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Abstract

Background. The definition of sudden unexpected death (SUD) in patients with advanced cancer near the end of life (EOL) was unclear.

Methods. This study was conducted as a single-center retrospective analysis. We analyzed 1,282 patients who died of advanced cancer from August 2011 to August 2019 retrospectively. We divided into patients who died within 24 h after the acute change of general condition or others and analyzed risk factors by a multiple logistics method. The reason for SUD was found, the reason is detected by using an electronic medical record retrospectively. The risk factors in SUD were analyzed using age, sex, EOL symptom and treatment, the primary site of cancer, metastatic site of cancer, comorbidly, chemotherapy, and Eastern Cooperative Oncology Group Performance Status. The primary endpoint was to identify the frequency and risk factors of SUD in patients with advanced cancer near the EOL.

Results. As a background, the median age is 73 years old, 690 males, 592 females, 227 gastroesophageal cancers, 250 biliary pancreatic cancers, 54 hepatocellular carcinomas, 189 colorectal cancer, 251 lung cancers, 71 breast cancers, 58 urological malignancies, 60 gynecological malignancies, 47 head and neck cancer, 31 hematological malignancies, and 22 sarcomas. The number of patients who died suddenly was 93 (7.2%) at EOL. In a multivariate analysis, Age (ORs 0.619), sex (ORs 1.700), patients with EOL delirium (ORs 0.483), nausea and vomiting (ORs 2.263), 1L or more infusion (ORs 3.479), EOL opioids (ORs 0.465), EOL sedations (ORs 0.339), and with cardiac comorbidity (ORs 0.345) were independent risk factors.

Conclusions. The frequency of patients who died suddenly was 7.2% ($n = 93$) at EOL. Age, sex, EOL symptom, EOL treatment, and cardiac comorbidity were independent risk factors in patients with advanced cancer near the EOL. Information on these risk factors is useful to explaining their EOL in advance.

Introduction

The disease trajectories are relatively similar in diseases and can be divided into four categories according to each disease group (Lunney et al., 2002, 2003). The trajectories of the end of life (EOL) stages in patients with advanced cancer are characteristic and easier to predict those life expectancies than those with other diseases. Thus, some scales to predict life expectancies in patients with advanced cancer have been developed (Maltoni et al., 1999; Morita et al., 1999a; Bridget et al., 2011; Baba et al., 2015; Uneno et al., 2017; Hamano et al., 2018). There are even a few studies in the context of resuscitation and autopsy of sudden changes (Nauck and Alt-Epping, 2008), but there are no studies of sudden death after acute change pathologically as empirical data. We call such cases a sudden unexpected death (SUD), but it has been difficult to define from what point the acute phase begins and to make it a subject of research. In Japan, there are two studies about SUD in hospice and palliative care units (Tsuneto et al., 1996; Morita et al., 1999a, 1999b), but "a sudden change" was defined vaguely as a case of death within 1–2 days due to an unexpected sudden change rather than a minor deterioration in the natural course of the disease. In a prospective study conducted at Yodogawa Christian Hospital Hospice in 1993, 47 (23%) of the 206 patients who died suddenly. Bleeding, pneumonia, respiratory failure, and gastrointestinal perforation were the most common causes of sudden changes (Tsuneto et al., 1996). In a prospective observational study at Seirei Mikatahara Hospital Hospice in 1996, 79 (42%) of the 186 who died due to sudden changes. In this study, pneumonia, aspiration, gastrointestinal bleeding, liver bleeding, and gastrointestinal perforation were encountered as causes of sudden changes (Morita et al., 1999b). In a recent study, MD Anderson Cancer Center reported about surprise questions in which doctors are asked if they are surprised by the sudden death of a patient. According to this report, 10% of the patients died suddenly without any change in vital signs or anything else, which surprised the doctors (Bruera et al., 2015). The frequency and risk factors of SUD in patients

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with advanced cancer near the EOL was unclear, therefore, the objective of this study was to identify frequency and risk factors in patients who died within 24 h due to the sudden change in the general condition.

Methods

Study design and patients

This study was conducted as a single-center retrospective analysis. We analyzed all patients who died of advanced cancer, brain tumors, or advanced hematological malignancies from August 2011 to August 2019 at Mitsubishi Kyoto Hospital. Patients aged 20 years or older and diagnosed with advanced cancer with metastatic and recurrence states were included.

Endpoints

The primary endpoint of this study was to identify risk factors in patients who died within 24 h due to the sudden change as SUD. We divided into patients of SUD and non-SUD and analyzed risk factors by a multiple logistics method. The reason for SUD was found, the reason is detected by using an electronic medical record retrospectively. The risk factors in SUD were analyzed using age, sex, EOL symptom and treatment, primary site of cancer, metastatic site of cancer, comorbidly, palliative referral, chemotherapy, Eastern Cooperative Oncology Group Performance Status, EOL symptoms, and EOL treatment details. With respect to EOL symptoms, our palliative care physician took care of each patient as a daily clinical practice. Since the knowledge of previous studies in SUD is scarce, we selected explanatory variables that are considered clinically important in relation to the explained variables, mainly based on variables treated in prognostic models for the terminal stage and clinical judgment. Delirium was diagnosed using the confusion assessment method (Inoue et al., 1990). The diagnoses of cancer pain, dyspnea, nausea and vomiting, and fatigue were determined based on clinical findings. The prevalence of distressing symptoms and details of EOL treatments were evaluated during the 3 days prior to death. We defined continuous deep sedation as the continuous use of sedatives to relieve intolerable and refractory symptoms with a total loss of patient consciousness until death (Morita et al., 2005). The number of opioids administered was recorded in terms of the oral morphine-equivalent dose.

Statistical analysis

Time of the event curves was calculated using the Kaplan–Meier method and compared using log-rank tests. The statistical influence as odds ratios (ORs) and 95% confidence intervals (CIs) was presented and interpreted based on multiple logistic regression models. A p-value < 0.05 was considered statistically significant. All analyses were performed using the R version 3.6.2. for OS X 10.11.

Ethical considerations

The study was conducted in accordance with the ethical requirements of the Declaration of Helsinki and the ethical guidelines for epidemiological research, presented by the Ministry of Health, Labor and Welfare of Japan. The hospital institutional review board approved this study.

Results

Patients' background

As a background, the median age is 73 years old, 690 males, 592 females, 227 gastroesophageal cancers, 250 biliary pancreatic cancers, 54 hepatocellular carcinomas, 189 colorectal cancer, 251 lung cancers, 71 breast cancers, 58 urological malignancies, 60 gynecological malignancies, 47 head and neck cancer, 31 hematological malignancies, and 22 sarcomas. The number of patients who died suddenly were 93 (7.2%) at the EOL (Table 1).

The reason for sudden unexpected death

There was no pathological autopsy or autopsy imaging after death. At the time of death, the cause of death could be estimated in 21 cases of aspiration, 10 cases of pulmonary embolus, 10 cases of epileptic seizure, 7 cases of intestinal perforation, 6 cases of gastrointestinal bleeding, 4 cases of DIC, 2 cases of hypoglycemia, 1 case of tumor bleeding, 1 case of carotid artery perforation, and 31 cases of other unknown causes.

Risk factors in a univariate analysis

Age (ORs 0.565, 95% CIs 0.342–0.934), sex (ORs 1.713, 95% CIs 1.069–2.743), patients with EOL delirium (ORs 0.485, 95% CIs 0.279–0.844), EOL nausea and vomiting (ORs 2.413, 95% CIs 1.194–4.874), EOL fatigue (OR 0.581, 95% CIs 0.320–1.052) and 1L or more daily infusion (ORs 3.630, 95% CIs 1.871–7.042), EOL opioids (ORs 0.458, 95% CIs 0.215–0.976), EOL sedation (ORs 0.348, 95% CIs 0.161–0.750), and patients with cardiac comorbidity (ORs 0.315, 95% CIs 0.120–0.823) were independent risk factors (Table 2).

Risk factors in a multivariate analysis

Age (ORs 0.619, 95% CIs 0.392–0.976), sex (ORs 1.700, 95% CIs 1.079–2.677), patients with EOL delirium (ORs 0.483, 95% CIs 0.280–0.833), nausea and vomiting (ORs 2.263, 95% CIs 1.145–4.474), 1L or more infusion (ORs 3.479, 95% CIs 1.814–6.673), EOL opioids (ORs 0.465, 95% CIs 0.224–0.968), EOL sedation (ORs 0.339, 95% CIs 0.160–0.722), and with cardiac comorbidity (ORs 0.345, 95% CIs 0.135–0.878) were independent risk factors (Table 3).

Discussion

Because of the definition of SUD was patients who died within 24 h of the sudden change, the rate of SUD was lower than in other previous studies. Because this study was retrospective, it may have underestimated the detection of sudden changes. It is difficult to detect the cause of death in cases of SUD in the EOL stage. There are few opportunities to do autopsies or autopsy imaging after the death of a cancer patient unless the family wishes to do so after the SUD in Japan. However, the details on the cause of SUD were similar to those reported in the past study.

In this study, age, sex, patients with EOL delirium, nausea and vomiting, 1L or more infusion, opioids, sedation, and cardiac comorbidity were independent risk factors in patients with advanced cancer near the EOL. Young, males were risk factors because they are more likely to continue systemic anticancer therapy (SACT) near the EOL because of their social roles. It is known that forcing patients to take SACT when their general condition

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Table 1. Patients' backgrounds

		All patients $N = 1,282$	Sudden unexpected death (+) $N = 93$	Sudden unexpected death (–) $N = 1,189$
Age	70 y.o>=/<70	777	50	727
Sex	male/female	690	59	631
End-of-life pain	+/–	322	22	300
End-of-life delirium	+/–	391	18	373
End-of-life nausea	+/–	81	13	68
End-of-life fatigue	+/–	318	17	301
End-of-life dyspnea	+/–	235	11	224
Infusion (daily)	1L>=/<1L	67	15	52
End-of-life opioids	60 mg>=/<60 mg	241	9	232
End-of-life sedation	+/–	266	7	259
Primary Cancer Site				
Head and neck cancer	+/–	55	5	50
Upper abdominal cancer	+/–	529	48	481
Thorax cancer	+/–	322	14	305
Lower abdominal cancer	+/–	307	20	287
Metastatic Site				
Liver	+/–	384	22	362
Lung	+/–	358	15	343
Central nerve system	+/–	116	7	109
Bone	+/–	205	10	105
Peritoneum	+/–	346	30	316
Comorbidity	+/–			
Cardiac	+/–	181	5	176
Psychiatric	+/–	115	9	106
Respiratory	+/–	108	7	101
Diabetes mules	+/–	169	9	160
Referral from other institution	+/–	722	40	676
Systemic anticancer therapy	+/–	773	60	713
Molecular targeting agents	+/–	249	21	228
Immune checkpoint inhibitors	+/–	87	5	82

worsens their prognosis at EOL (Hiramoto et al., 2019, 2021). The side effects and invasiveness of SACT are often thought to cause rapid changes. EOL delirium, high doses of opioids, and sedations are associated with a low risk of SUD because the gradual weakness of the patient is likely to be observed in the natural course at EOL. Although there is concern about an increase in aspiration due to the decreased level of consciousness caused by EOL delirium, opioids overdose, and sedations, there is no need to hesitate when these therapeutic interventions are necessary near the EOL because at least sudden deaths do not increase with interventions such as opioids and sedations (Maeda et al., 2016). Relatively large infusions of fluids are considered a risk factor for SUD, but this may be the result of what clinicians consider believe that sudden changes rather than gradually worsen must be treated aggressively. Nausea and vomiting can be a risk factor for aspiration because vomit can easily enter the respiratory tract when the patient is lying in bed, especially when the level of consciousness is low. It is not known whether reducing oral intake or avoiding drinking water can reduce this aspiration risk, but it may be better to inform patients and their families of the risk in advance practically. The result of low risk for SUD in patients with cardiac comorbidity was paradoxical. It is generally believed that patients with concomitant cardiac disease are more likely to develop cardiovascular events. This is because electrolyte abnormalities are common at EOL, and severe arrhythmias are a common cause of SUD. Although the use of immune checkpoint inhibitors and molecular targeted drugs was not associated with SUD, it is important to note that the situation may change in the future when the use of these drugs increases (Hiramoto et al., 2021).

Although it is still unclear whether it is possible to reduce the risk of sudden changes at EOL, it is better to explain the risk of sudden changes along with the gradual worsen of the patient's

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Table 2. Risk factors of sudden death in patients with advanced cancer near the end of life in univariate analysis

		Univariate analysis			
		Odds ratio	95% Confidence interval		*p*-value
Age	70 y.o>=/<70	0.565	0.342	0.934	0.026
Sex	male/female	1.713	1.069	2.743	0.025
End-of-life pain	+/−	0.917	0.537	1.567	0.025
End-of-life delirium	+/−	0.485	0.279	0.844	0.011
End-of-life nausea	+/−	2.413	1.194	4.874	0.014
End-of-life fatigue	+/−	0.581	0.320	1.052	0.073
End-of-life dyspnea	+/−	0.723	0.360	1.455	0.364
Infusion (daily)	1L>=/<1L	3.630	1.871	7.042	0.000
End-of-life opioids	60 mg>=/<60 mg	0.458	0.215	0.976	0.043
End-of-life sedation	+/−	0.348	0.161	0.750	0.007
Head and neck cancer	+/−	0.890	0.248	3.197	0.859
Upper abdominal cancer	+/−	0.820	0.318	2.118	0.682
Thorax cancer	+/−	0.530	0.183	1.536	0.242
Lower abdominal cancer	+/−	0.728	0.268	1.978	0.534
Liver metastasis	+/−	0.598	0.344	1.040	0.069
Lung metastasis	+/−	0.558	0.297	1.049	0.070
Brain metastasis	+/−	0.783	0.312	1.967	0.603
Bone metastasis	+/−	0.572	0.275	1.187	0.134
Peritoneal metastasis	+/−	0.855	0.490	1.492	0.581
Cardiac comorbidity	+/−	0.315	0.120	0.823	0.018
Psychiatric comorbidity	+/−	0.956	0.441	2.072	0.910
Lung comorbidity	+/−	1.029	0.433	2.443	0.949
Diabetes mules	+/−	0.749	0.353	1.589	0.452
Systemic anticancer therapy	+/−	1.053	0.637	1.741	0.840
Molecular targeting agents	+/−	1.110	0.651	1.893	0.702
Immune checkpoint inhibitors	+/−	0.734	0.277	1.945	0.534

Table 3. Risk factors of sudden death in patients with advanced cancer near the end of life in multi-variate analysis

		Multivariate analysis			
		Odds ratio	95% Confidence interval		*p*-value
Age	70 y.o>=/<70	0.619	0.392	0.976	0.039
Sex	male/female	1.700	1.079	2.677	0.022
End-of-life delirium	+/−	0.483	0.280	0.833	0.009
End-of-life nausea	+/−	2.263	1.145	4.474	0.019
Infusion (daily)	1L>=/<1L	3.479	1.814	6.673	0.000
End-of-life opioids (daily)	60 mg>=/<60 mg	0.465	0.224	0.968	0.041
End-of-life sedation	+/−	0.339	0.160	0.722	0.005
Cardiac comorbidity	+/−	0.345	0.135	0.878	0.026

overall functions as they weaken. Although it is still unclear whether it is possible to reduce the risk of SUD at EOL, it is better to explain those along with the gradual deterioration of the patient's overall vital functions as they weaken. However, it is better to explain the risk of SUD as well as the gradual deterioration of the patient's overall vital functions when they become weaker.

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Furthermore, explaining this information in advance may help reduce grief in the family and avoid burnout in the medical staff when SUD occurs. Risk factors such as age, gender, nausea and vomiting at EOL, and cardiac comorbidity may help predict the likelihood of SUD.

The limitation of this study is a retrospective study with reference to medical record data, it is so highly possible that "sudden changes" cannot be detected accurately. Second, because it is a retrospective cohort study, cause and effect relationships may not be appropriate. It is possible that they are looking at outcomes, especially for opioids at EOL. Third, since the study was conducted at a single facility, it is difficult to generalize the results. It is hoped that a multicenter prospective study will be conducted to address these problems.

Conclusion

The frequency of patients who died suddenly was 7.2% ($n = 93$) at EOL. Age, sex, delirium, nausea and vomiting, 1L or more infusion, opioids, sedation, and cardiac comorbidity were independent risk factors in patients with advanced cancer near the EOL. Information on these risk factors is useful to explaining about their EOL in advance.

Conflict of interest. There are no conflicts of interest to declare.

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