Effect of anamorelin treatment duration on survival of patients with cancer cachexia: A retrospective study

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Abstract. Real-world data on the effectiveness of anamorelin in managing cancer cachexia remains limited, particularly as its availability is currently restricted to Japan. In the present study, anamorelin use in cancer cachexia management was retrospectively evaluated, focusing on patient characteristics and survival after both short- and long-term use. Patients prescribed anamorelin between August 2021 and January 2024 at the Saitama Canc2er Center (Ina, Japan) were included. Medical records were reviewed to collect baseline characteristics at anamorelin treatment initiation. The patients were divided into two groups: short- and long-treatment groups (STT and LTT, respectively). Overall, 60 and 69 patients were included in the STT and LTT groups, respectively. Significant intergroup differences were found in age (P=0.021), gastric cancer incidence rate (P=0.013), albumin level of <3.5 g/dl (P=0.044) and Eastern Cooperative Oncology Group performance status score (P=0.008). The longest median time from diagnosis to anamorelin treatment initiation was observed for colorectal cancer, while the longest median anamorelin treatment duration was observed for lung cancer. The median survival durations during anamorelin treatment were 49 and 142 days in the STT and LTT groups, respectively (P<0.001). The corresponding median survival durations after anamorelin treatment termination in the STT and LTT groups were 38 and 34 days (P=0.554), respectively. Anamorelin treatment duration influenced patient survival, with post-discontinuation survival being ~1 month, regardless of treatment length.

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Introduction

Cancer cachexia, a syndrome characterized by severe weight loss and muscle depletion, is of significant concern in patients with advanced cancer. Its incidence rate ranges from 50-80%, and markedly affects mortality, accounting for up to 20% of cancer-related deaths (1,2). In Japan, the European Palliative Care Research Collaborative criteria and European Society for Medical Oncology criteria are used in cancer cachexia management as no specific guidelines exist for this condition in the country (3,4).

Cancer cachexia is a complex syndrome involving various factors, including skeletal muscle loss, activation of inflammatory cytokines, metabolic disturbances due to insulin resistance, and increased catabolism of hyperlipidemia (5,6). Cancer cachexia progression may result in irreversible malnutrition, significantly reducing the activities of daily living and quality of life, leading to worse prognosis. As metabolic disorders progress, effective nutrient utilization is impaired; hence, multidisciplinary interventions, such as nutritional therapy, exercise, and pharmacotherapy are essential from the early stages of cancer cachexia (6,7). Promising pharmacological approaches for cachexia management include ghrelin agonists, beta-blockers, beta-adrenergic agonists, androgen receptor agonists, and antimyostatin peptides (8). However, their clinical application in cancer cachexia management remains limited, and their use is associated with potential adverse effects, necessitating cautious application.

Anamorelin, the first oral small-molecule ghrelin-like agent worldwide, became available in Japan in 2021 and was anticipated to alleviate cancer cachexia-related weight loss and anorexia (9). Ghrelin, a growth hormone secretagogue primarily secreted in the stomach, acts on appetite-promoting neurons in the hypothalamus and indirectly stimulates muscle protein synthesis by stimulating the secretion of the growth hormone and insulin-like growth factor 1 in the liver (10-12). Additionally, ghrelin is believed to counteract cancer cachexia through multiple mechanisms, including its anti-inflammatory effects and inhibition of muscle atrophy (13,14). Anamorelin is indicated for cancer cachexia management in patients with non-small cell lung, gastric, pancreatic, and colorectal cancers.

Notably, its use necessitates caution owing to potential adverse events, including fatal arrhythmias and hyperglycemia (15).

Considering that anamorelin is a Japan-specific medicine, real-world data on its use remain limited. Furthermore, although early intervention is recommended for cancer cachexia, research on the optimal timing of anamorelin administration is scarce, highlighting the need for further investigation. Therefore, the aim of this retrospective study was to investigate the use of anamorelin in cancer cachexia treatment and examine the relationship between treatment duration and patient survival.

Patients and methods

Study design and end point. This retrospective study included patients who were prescribed anamorelin between August 2021 and January 2024 at the Saitama Cancer Center, Japan. Eligible patients had unresectable, advanced, or recurrent non-small cell lung, gastric, pancreatic, or colorectal cancers with cachexia, defined by >5% weight loss and anorexia within 6 months, along with at least two of the following symptoms: i) fatigue or malaise; ii) muscle weakness; and iii) one or more of the following conditions: C-reactive protein (CRP) level >5 mg/l, hemoglobin level <12 g/dl, and serum albumin level <3.2 g/dl. The inclusion criteria align with the clinical indications for prescribing anamorelin. Inclusion criteria were retrospectively assessed using electronic medical records, including documented weight loss percentages, clinical notes on anorexia, and laboratory test results for cachexia-related symptoms (e.g., CRP, hemoglobin, and serum albumin levels). This review ensured consistent application of the eligibility criteria. Fig. 1 depicts the study flowchart. Because the anamorelin package insert states that its efficacy is determined in the third week of administration, patients were classified into two groups: short-term treatment (STT; discontinuation within 3 weeks) and long-term treatment (LTT; >3 weeks). The primary endpoint was to evaluate the effect of treatment duration on the survival of patients with cancer cachexia. The secondary endpoint was to investigate the time from diagnosis to treatment initiation for each type of cancer and the duration of anamorelin administration.

Data extraction. The following baseline patient characteristics at the initiation of anamorelin treatment were extracted from the patient medical records: age; sex; primary cancer site; Eastern Cooperative Oncology Group (ECOG) performance status (PS) score; albumin, CRP, and hemoglobin levels; Glasgow Prognostic Score (GPS); date of diagnosis of stage IV, inoperable advanced, or recurrent cancer; history of surgery for gastric cancer; reason for discontinuation of anamorelin; start and end dates of anamorelin treatment; reason for completion of anamorelin treatment; and date of death or last hospital visit. The ECOG PS 0-2 classification, which was previously used as a selection criterion in national and international phase III trials, was used as the standard in this study (16). The GPS was calculated using the following formula: CRP level <10 mg/l and albumin level ≥3.5 g/dl, GPS=0; CRP level >10 mg/l, GPS=1; and CRP level >10 mg/l and albumin level <3.5 g/dl, GPS=2 (17).

Reasons for discontinuation of anamorelin were categorized as treatment ineffectiveness, difficulty in medication intake, psychological burden of medicine intake, death, and other reasons. Treatment ineffectiveness was determined clinically, primarily on weight changes and patient-reported symptoms, such as persistent anorexia, despite continued treatment. Difficulty in medication intake was identified from medical records describing swallowing difficulties (dysphagia), nausea, or a general decline in physical condition hindering oral intake. The psychological burden of taking the medicine was assessed through medical records of patient-reported concerns, including reluctance to take oral medication owing to anxiety or subjective distress related to medication intake.

Statistical analysis. The Fisher's exact test was used to compare nominal variables, whereas the Mann-Whitney *U* test was used to compare continuous variables. Outliers were defined as values exceeding the third quartile by more than 1.5 times the interquartile range. Overall survival curves were generated using the Kaplan-Meier method, and differences in the curves were compared using a log-rank test. Patients were censored if they met one of the following criteria: i) overall survival of >365 days or ii) data not traceable owing to other reasons, including hospital transfer. Statistical analyses were performed using EZR ver. 1.66 (18), with a P-value of <0.05 considered statistically significant.

Results

Patient characteristics. In total, 129 patients were included in this study, with 60 and 69 patients in the STT and LTT groups, respectively (Table I). Compared with the LTT group, the STT group had significantly more patients with gastric cancer (P=0.013) or an albumin level of <3.5 g/dl (P=0.044). In contrast, the LTT group had a significantly higher number of older patients (P=0.021) and those with an ECOG PS of 0-2 (P=0.008) than the STT group. No significant differences were observed between the two groups with respect to other patient characteristics. A comparison of the number of patients who underwent surgery for gastric cancer showed no significant differences between the groups (STT group: 23.1% vs. LTT group: 20.0%, P=1.0). The most common reason for termination of anamorelin treatment in both groups was treatment ineffectiveness (STT group, 33.3%; LTT group, 21.7%). In the STT group alone, the reasons for termination were difficulty in medication intake (23.3%) and the psychological burden of medication intake (11.7%), while in the LTT group, the reasons were death (13.0%) and the psychological medication intake (10.1%). Among patients in the STT group who discontinued owing to difficulty in medication intake, the primary factors were dysphagia, nausea, and general deterioration in physical condition. Importantly, no discontinuations were attributed to side effects of anamorelin.

Timing of anamorelin initiation and duration of treatment. Fig. 2 shows the time between diagnosis and anamorelin treatment initiation. The median time from the date of diagnosis to the start of anamorelin treatment was the longest among patients with colorectal cancer (489 days), followed by those with non-small cell lung cancer (244 days), gastric cancer (222 days), and pancreatic cancer (99 days). The anamorelin

Table I. Characteristics of the study patients.

Characteristics	STT group (n=60)	LTT group (n=69)	P-value
Median age, years (range)[a]	71 (36-84)	73 (50-90)	0.021
Male, n (%)[b]	40 (66.7)	52 (75.4)	0.331
Primary cancer, n (%)[b]			
Gastric cancer	26 (43.3)	15 (21.7)	0.013
Colorectal cancer	5 (8.3)	6 (8.7)	>0.999
Pancreatic cancer	14 (23.3)	22 (31.9)	0.328
NSCLC	15 (25.0)	26 (37.7)	0.134
ECOG PS score, n (%)[b]			
0-2	39 (65.0)	59 (85.5)	0.008
3-4	21 (35.0)	10 (14.5)	0.008
Median serum albumin level, g/dl (range)[a]	3.1 (2.0-4.7)	3.4 (1.5-4.8)	0.095
Serum albumin level <3.5 g/dl, n (%)[b]	43 (71.7)	36 (52.2)	0.044
Median C-reactive protein level, mg/l (range)[a]	20.7 (0.1-305.2)	14.7 (0-257.9)	0.227
C-reactive protein level, n (%)[b]			
>10 mg/l	39 (65.0)	39 (58.0)	0.468
>5 mg/l	46 (76.7)	45 (65.2)	0.242
Median hemoglobin level, g/dl (range)[a]	11.0 (7.2-15.2)	10.4 (7.7-15.7)	0.404
Hemoglobin level <12.0 g/dl, n (%)[b]	41 (68.3)	52 (75.4)	0.326
Glasgow prognostic score[c], n (%)[b]			
0	21 (35.0)	29 (42.0)	0.468
1	8 (13.3)	14 (20.3)	0.350
2	31 (51.7)	25 (36.2)	0.109
Median time from diagnosis to treatment initiation, days (range)[a]	279 (0-2486)	193 (0-3122)	0.286
Median administration period, days (range)[a]	9.5 (0-19)	44.5 (21-444)	<0.0001

[a]Mann-Whitney U test, [b]Fisher's exact test. [c]For 1 case of LTT, details are unknown due to treatment initiation at another hospital. The P-values refer to the comparison between the STT group and the LTT group. All P-values calculated using Fisher's exact test were based on a 2x2 contingency table comparing the presence or absence of each characteristic between the STT and LTT groups. STT, short-term treatment; LTT, long-term treatment; NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

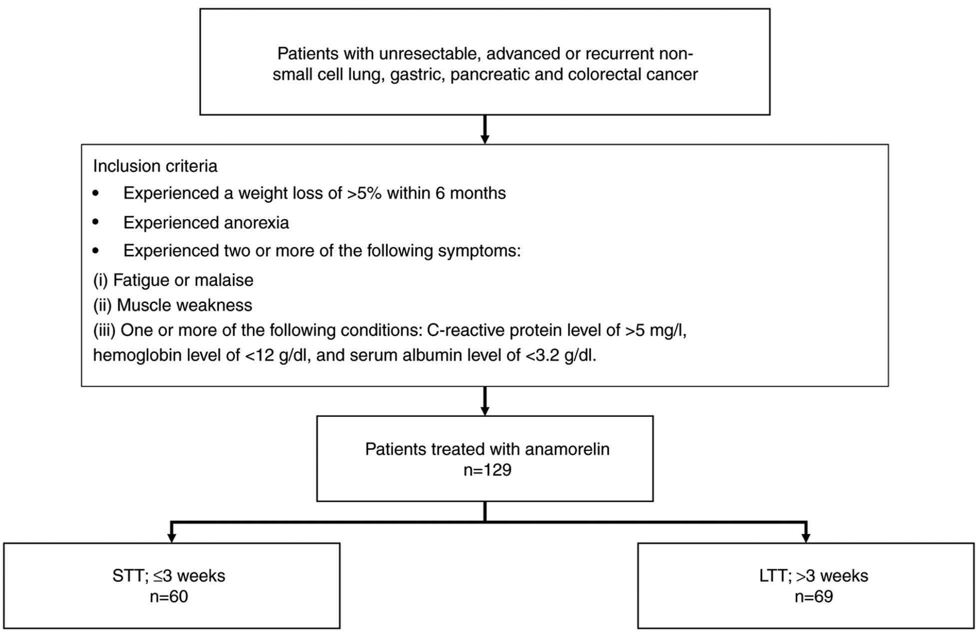

Figure 1. Study flow chart. STT, discontinuation within 3 weeks; LTT, >3 weeks. LTT, long-term treatment; STT, short-term treatment.

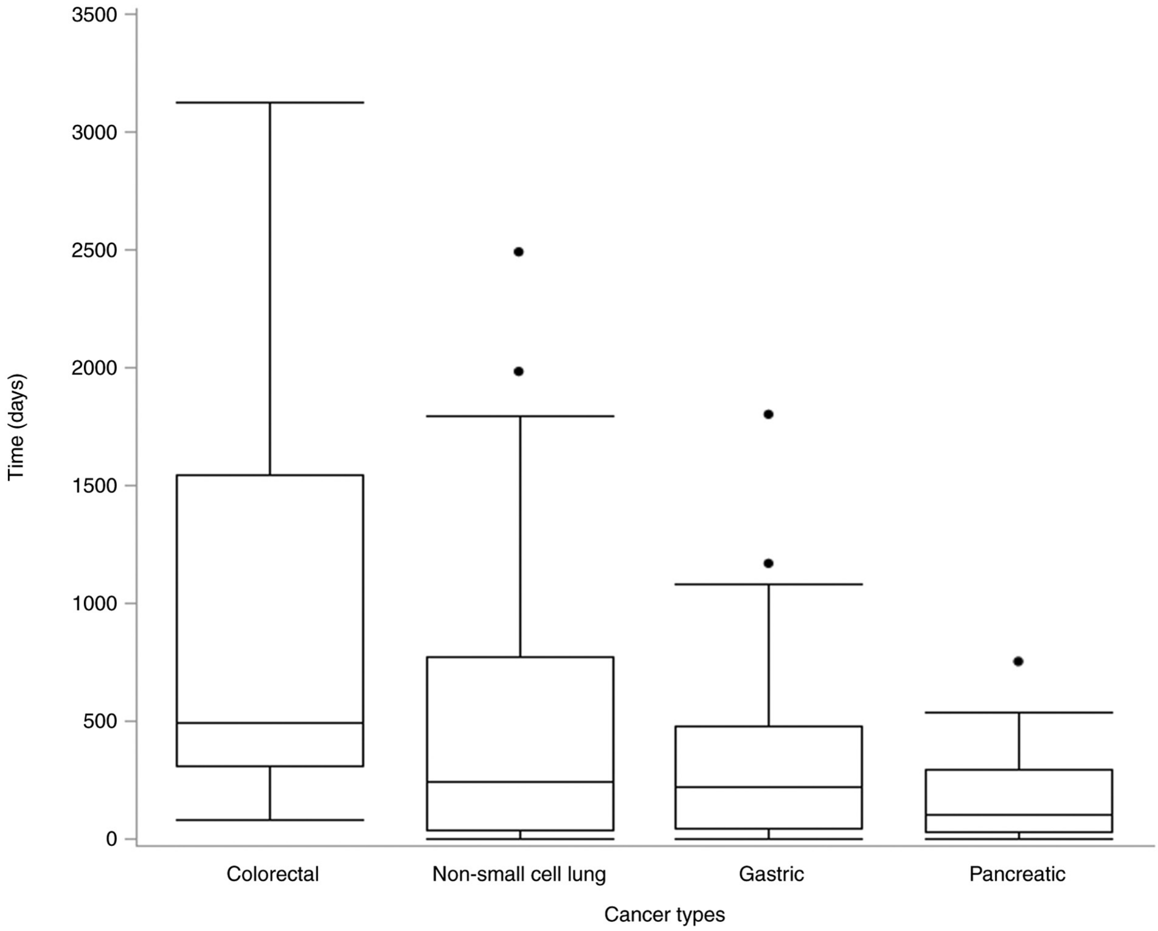

Figure 2. Time from the diagnosis of recurrent or inoperable cancer to anamorelin treatment initiation. The individual points plotted beyond the whiskers of the box plot represent outliers.

treatment period is shown in Fig. 3. The median duration of anamorelin treatment was the longest for lung cancer (34 days), followed by that for colon cancer (28 days), pancreatic cancer (22 days), and gastric cancer (14 days). Three cases with non-small cell lung cancer (treatment durations: 240, 444, and 773 days), eight with stomach cancer (treatment durations: 90, 106, 126, 146, 167, 223, 285, and 292 days), and four with pancreatic cancer (treatment durations: 70, 87, 138, and 285 days) were analyzed as outliers.

Period from anamorelin treatment initiation to death or last hospital visit. The overall survival rate from the start of anamorelin treatment to death or last hospital visit is shown in Fig. 4. The median survival durations were 49 days [95% confidence interval (CI), 36-80] and 142 days (95% CI, 85-201) in the STT and LTT groups, respectively, with the duration in the LTT group being significantly longer ($P<0.001$). The data of a patient in the LTT group were excluded from the analysis as the treatment end date was unknown.

Survival after completion of anamorelin treatment. The overall survival rate was defined as the number of days from the day after the last day of anamorelin treatment to the day of death or last hospital visit (Fig. 5). The median survival durations were 38 days (95% CI, 23-66 days) and 34 days (95% CI, 26-61 days) in the STT and LTT groups, respectively ($P=0.554$). The data of a patient in the LTT group were excluded from the analysis as the treatment end date was unknown.

Discussion

In this retrospective study, the use of anamorelin in managing cancer cachexia was examined, focusing on patient characteristics and survival during and after treatment. Age, gastric cancer, hypoalbuminemia, and ECOG PS score were identified as patient factors affecting treatment duration. While patients in the LTT group had significantly longer survival duration during treatment than those in the STT group, post-discontinuation survival did not differ significantly among groups, regardless of treatment duration. These findings suggested that anamorelin treatment duration can be a predictor of survival during treatment.

In this study, anamorelin was administered long term to patients with an ECOG PS score of 0-2. Our findings align with those of studies examining the efficacy of anamorelin in patients with pancreatic cancer with a poor ECOG PS score and studies investigating factors associated with the early discontinuation of anamorelin (19,20). This result suggests that patients with good ECOG PS scores may tolerate long-term anamorelin treatment. In this study, the LTT group had a higher number of older patients, possibly owing to the role of anamorelin in increasing sensitivity to ghrelin, which declines

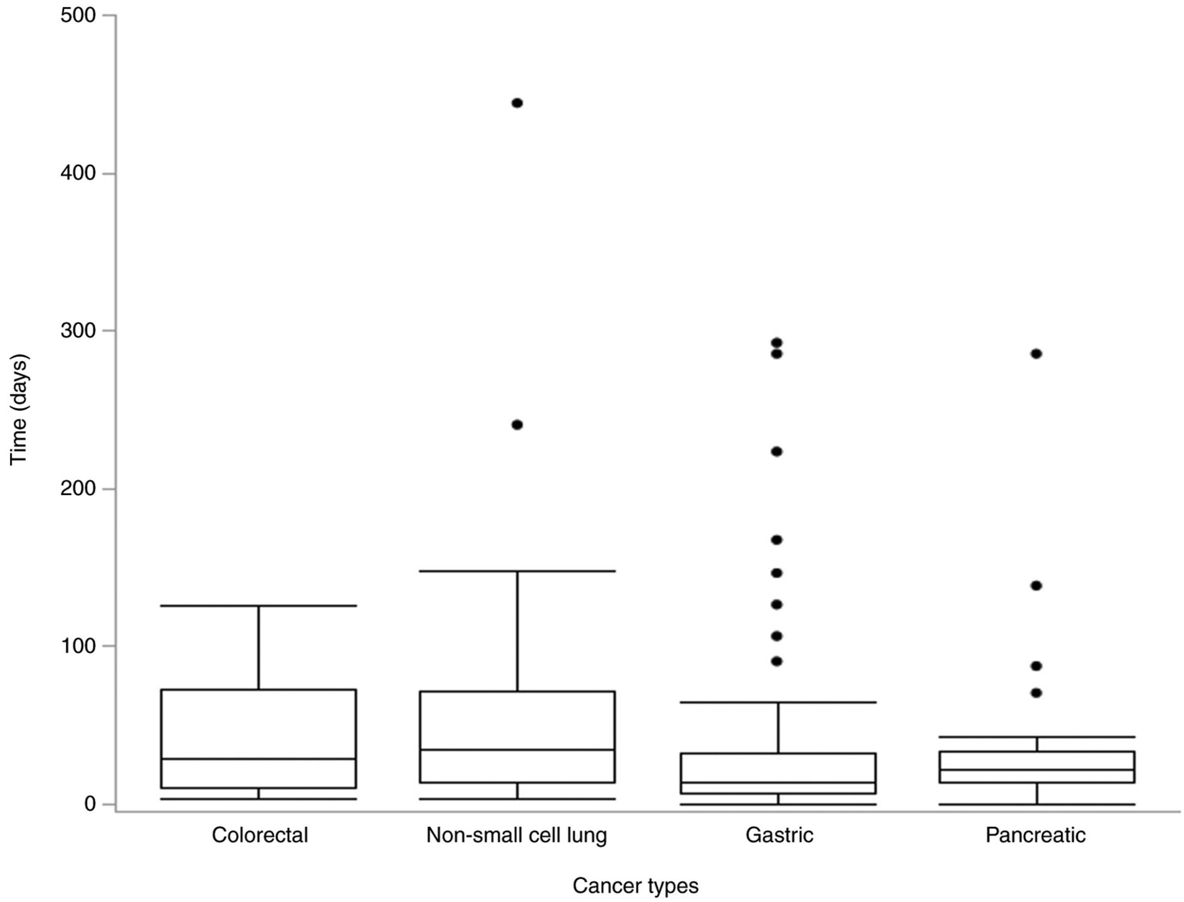

Figure 3. Anamorelin treatment duration. The individual points plotted beyond the whiskers of the box plot represent outliers.

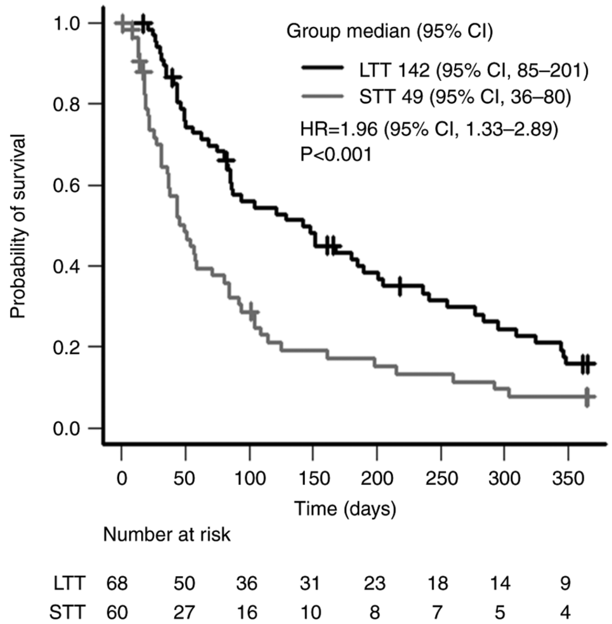

Figure 4. Kaplan-Meier curves for overall survival. The plus sign indicates censored data. HR, hazard ratio; LTT, long-term treatment; STT, short-term treatment.

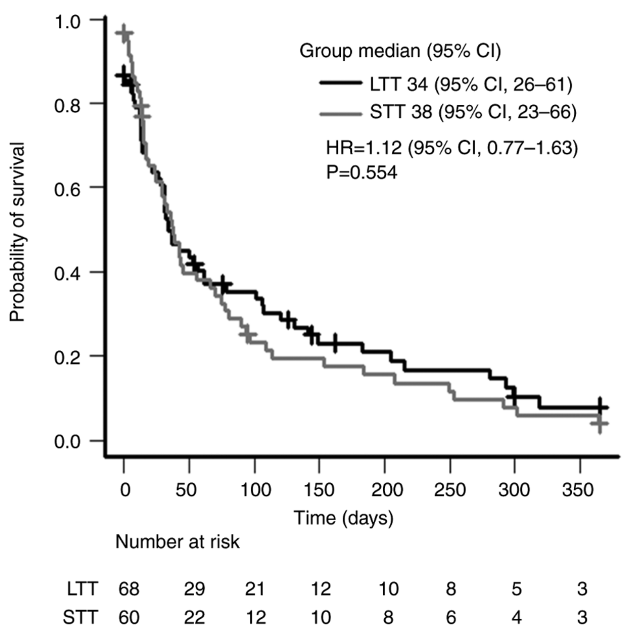

Figure 5. Kaplan-Meier curve for overall survival after termination of anamorelin treatment. The plus sign indicates censored data. HR, hazard ratio; LTT, long-term treatment; STT, short-term treatment.

with age and may activate relevant signaling pathways. Blood ghrelin levels generally decrease with age; however, the relationship between ghrelin and aging remains unclear, as existing studies have yielded conflicting results, warranting further investigation (21). Regarding cancer type, the STT group had a higher number of patients with gastric cancer.

Ghrelin is a peptide hormone produced and secreted mainly in the gastric body. Total gastrectomy reduces blood ghrelin levels by 10-30% and distal gastrectomy decreases these levels by 50-70% (22). In the present study, the surgical history of patients with gastric cancer was compared between the two groups; however, no effect of surgery on treatment duration was observed. This result suggests that factors beyond gastric preservation may have affected the duration of anamorelin treatment; however, further studies with a larger sample size are warranted to validate this. In addition, hypoalbuminemia was more common in the STT group, suggesting its potential as a predictive factor for treatment duration. Given that hypoalbuminemia is associated with reduced survival rate of patients with gastric cancer, it may contribute to considerably shorter treatment duration observed in this patient population (23). Further investigation into the interplay between cancer type and hypoalbuminemia using larger cohorts is warranted.

The median treatment duration tended to be shorter for non-small cell lung, colorectal, pancreatic, and gastric cancers, in that order. The results, except that of gastric cancer, were similar to those of the interim analysis of the post-marketing survey for anamorelin. Notably, the median treatment duration for gastric cancer was 14 days shorter in this study than the 29 days reported in the post-marketing survey (24). In addition, gastric cancer was associated with a high frequency of abnormal values compared with other cancer types, suggesting that additional factors may influence the duration of anamorelin administration in this context. Further detailed studies are warranted to investigate this.

Survival during anamorelin treatment was significantly shorter in the STT group than in the LTT group. Similar results were reported in a study involving a small number of cases (20). In this study, the reason for treatment discontinuation was also investigated, revealing that more patients in the STT group discontinued treatment because of medication intake difficulty. Therefore, it is recommended that anamorelin be prescribed to patients with a good ECOG PS score who can tolerate prolonged treatment. We found that the median survival duration after the completion of anamorelin treatment was approximately 1 month, regardless of the treatment duration. To the best of our knowledge, this is a novel finding. The predicted survival time for refractory cachexia is generally considered to be less than 3 months (3). However, this period has been established by experts as an empirical guideline and is not based on real-world data. Moreover, our study is the first to report survival after the discontinuation of anamorelin for cachexia. Based on our findings, determining whether anamorelin can be effective against refractory cachexia or whether the predicted survival period has been overestimated remains a subject for future research.

This study had several limitations. First, this was a single-center, retrospective, observational study conducted among Japanese patients, which may limit the generalizability and validity of its findings to a broader population. Second, limitations inherent to retrospective studies, such as selection and reporting bias cannot be ruled out. Third, the observed prolonged survival in the LTT group may have been influenced by immortal time bias, which is an inherent limitation of the study design. Although time-dependent analyses or sensitivity analyses could potentially address this issue, such approaches were not feasible in the present study owing to the retrospective nature of the data and limitations in the dataset structure. Specifically, making multiple assumptions regarding variable selection and the handling of missing data was difficult. Furthermore, prior studies have provided limited evidence regarding causal relationships in this context. Therefore, we decided not to perform sensitivity analyses, as they were unlikely to improve the robustness or reliability of our findings. We acknowledge this as a methodological limitation, and future studies should consider more refined analytical strategies to minimize the impact of immortal time bias. Fourth, patient characteristics and prognosis differ according to cancer type. Therefore, a cancer type-specific analysis would have been preferable. However, in this study, stratified analysis was challenging owing to statistical limitations owing to the limited number of patients with each cancer type. Additionally, although factors such as patient age, presence of gastric cancer, PS, and serum albumin levels may independently affect survival, considering the scope of the study, adjustments using propensity score matching or subgroup analysis were not feasible owing to the small sample size. Fifth, prognostic factors such as exercise therapy, nutritional support, and chemotherapy were not examined in this study. Hence, future studies addressing these limitations are warranted. Sixth, the applicability of our findings may be influenced by cultural, healthcare, and demographic differences. Variations in dietary habits, patient preferences, and perceptions of appetite loss could affect treatment adherence and efficacy. Differences in healthcare systems, including access to supportive care and nutritional interventions, may also impact real-world outcomes. Additionally, racial differences in drug metabolism and cachexia progression could influence treatment response. Finally, anamorelin is currently approved only in Japan, making it a drug unique to the Japanese healthcare system. Its clinical use remains geographically limited, and its applicability to other healthcare settings is unclear. Given these limitations, further studies are warranted to evaluate its effectiveness in diverse patient populations and different healthcare environments.

Notably, anamorelin is only approved in Japan, limiting its clinical applicability to other healthcare settings. To the best of our knowledge, no single-center study with a larger number of patients has been conducted, making our findings an important source of clinical information. Nevertheless, further investigation through a larger multicenter prospective study is warranted.

In conclusion, the study findings indicated that older patients with better ECOG PS scores exhibited a longer treatment duration, whereas those with gastric cancer and hypoalbuminemia had a shorter treatment duration. In addition, the duration of anamorelin treatment was reflected in the survival of patients; however, the main novel finding of this study was that the survival time after treatment discontinuation remained approximately one month, regardless of the length of treatment. Considering the limited information on the efficacy and safety of anamorelin, future multicenter prospective studies with relatively larger sample sizes are warranted.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MoS was the principal investigator. MiS, DT, TA, KT, TN and MoS planned the study protocol and performed data collection. MH, MiS and MoS performed data analysis. MiS and MoS wrote the first draft of the manuscript. MiS, MO and MoS supervised the study, contributed to the interpretation of data and approved the final draft. All authors commented on the previous versions of the manuscript. TA, KT, TN and MO confirmed the authenticity of the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board (IRB) of Saitama Cancer Center (IRB no. 1398; Ina, Japan), and all procedures were performed in accordance with The Declaration of Helsinki. The requirement for informed consent was waived by the IRB due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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