doi: 10.2490/prm.20240031 Progress in Rehabilitation Medicine 2024; Vol. 9, 20240031

ORIGINAL ARTICLE

Relationship between Survival Days, Cancer Cachexia, and Activities of Daily Living in Palliative Cancer Patients Undergoing Rehabilitation

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Objectives: Cancer cachexia has many effects on physical function and causes a decline in activities of daily living (ADL). Therefore, rehabilitation programs should be structured according to the degree of cancer cachexia. Currently, the evaluation of cancer cachexia is mainly based on body mass. However, there is no report on the use of the modified Glasgow Prognostic Score (mGPS) to evaluate the degree of cancer cachexia and survival prognosis in palliative cancer patients for whom rehabilitation has been prescribed. This study used mGPS to examine the prevalence of cancer cachexia in palliative cancer patients undergoing rehabilitation and the impacts of cancer cachexia, ADL, and complications on survival. **Methods:** The participants included 135 palliative cancer patients who were admitted to the hospital and underwent rehabilitation between 2020 and 2022. Cancer cachexia classification by mGPS was conducted, and logistic regression analysis was used to examine factors affecting the survival of palliative cancer patients undergoing rehabilitation. **Results:** The patients were grouped as follows: 6 (4.4%) normal, 13 (9.6%) undernourished, 12 (9.0%) pre-cachexia, and 104 (77.0%) refractory cachexia. Logistic regression analysis showed that the mGPS and BI affected survival. **Conclusions:** In a cohort of palliative cancer patients undergoing rehabilitation, 86% had cachexia. mGPS and BI were associated with survival outcomes. Combination of mGPS classification with ADL assessment may provide meaningful prognostic information in these patients.

Key Words: activities of daily living; cachexia; overall survival; palliative cancer; rehabilitation

INTRODUCTION

Cancer cachexia is defined as "a multifactorial condition characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment".[1] Patients with cancer cachexia have decreased physical function,[2] are less likely to tolerate cancer treatment,[3] and have decreased overall survival.[4] Regarding the effects of rehabilitation on cancer patients with cachexia, exercise therapy is reported to lead to anti-inflammatory effects in skeletal muscles.[5] Furthermore, exercise therapy improves the physical function and quality of life of cancer patients and reduces the burden on caregivers.[6–9] When implementing rehabilitation for palliative cancer patients, the degree of cancer cachexia should be appropriately assessed, and exercise therapy should be

Received: April 22, 2024, Accepted: September 10, 2024, Published online: October 2, 2024
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considered.

The European Palliative Care Research Collaborative (EPCRC) has published criteria for the assessment of cancer cachexia based on a report by Fearon et al.[1] However, it has been pointed out that weight assessment alone may not be sufficient to assess cachexia and that the EPCRC criteria are vague and difficult to interpret. Previous research has shown that standard blood tests for the presence of multiple factors that characterize cachexia, such as high C-reactive protein (CRP) and low serum albumin (Alb) levels, in addition to body mass, should be evaluated.[10] In 2023, the Asia Working Group for Cachexia proposed diagnostic criteria for cachexia in Asian populations. In addition to the assessment of weight and body mass index, CRP is one of the criteria.[11]

The Glasgow Prognostic Score (GPS) evaluates cancer cachexia using blood biomarkers, including Alb and CRP levels.[12] The modified Glasgow Prognostic Score (mGPS) with adjusted CRP cutoff values also incorporates CRP and Alb. It has an independent prognostic value for patients with solid tumors and head and neck cancer[13–15] and is a simple method of assessing cancer cachexia using blood tests. However, no study has used mGPS to evaluate the degree of cancer cachexia and survival prognosis in palliative cancer patients for whom rehabilitation was prescribed. In this study, we investigated the incidence of cachexia at the start of a rehabilitation intervention in palliative cancer patients using the mGPS. We also examined factors affecting survival prognosis in palliative cancer patients.

MATERIALS AND METHODS

Patients

The study included 135 incurable cancer patients (best supportive care patients) who were admitted to our hospital's general wards between February 2020 and November 2022. All included patients were prescribed physical therapy by a palliative care physician, and their survey data were available for extraction.

A palliative care physician used the following criteria to prescribe physical therapy: the hospitalized patient wants to undergo rehabilitation, the goal of therapy is to improve and maintain activities of daily living (ADL), and the goal is to relieve the hospitalized patient's pain. All hospitalized patients who met any of these criteria were included as subjects of this study.

Ethical Considerations

All procedures were performed under an approved protocol and in accordance with the ethical standards of the Kanamecho Hospital Ethics Committee (Approval No. 23001) and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Because the design of our study was retrospective without intervention, the opt-out method was used instead of informed consent.

Clinical Parameters

The following data were recorded for all patients: sex, age, primary cancer site (breast cancer or other), cancer cachexia assessment, Barthel Index (BI), and comorbidities. Measurements and assessments were conducted at the start of rehabilitation.

Overall Survival

Based on previous research,[16–18] patients were classified according to whether they survived more than 90 days (≥90 day survival group) or less than 90 days (<90 day survival group).

Cancer Cachexia Assessment

Cancer cachexia was evaluated using mGPS.[19] In this assessment, levels of Alb (3.5 g/dL) and CRP (0.5 mg/dL) are used as cutoff values. Patients may be classified into four categories: normal (Alb ≥3.5 g/dL, CRP<0.5 mg/dL); pre-cachexia (Alb≥3.5 g/dL, CRP>0.5 mg/dL); low nutrition (Alb<3.5 g/dL, CRP<0.5 mg/dL); and refractory cachexia (Alb<3.5 g/dL, CRP>0.5 mg/dL).[20] The patients were classified into two groups: a normal/low-nutrition group and a pre-cachexia/refractory cachexia group.

Activities of Daily Living

Patient ADL status was evaluated using BI.[21] This index is calculated based on the following ten items: feeding, grooming, bathing, toileting, dressing, mobility, transfer, stair climbing, bowel control, and bladder control. Higher overall BI reflects a greater level of functional independence. In this study, BI was classified into two groups (≥45 group and <45 group) based on the BI severity classification of previous studies.[22,23]

Comorbidity

Comorbidity was assessed using the Charlson Comorbidity Index (CCI).[24] The CCI is calculated as the sum of 19 conditions that are weighted depending on the relative risk in 1-year mortality. Based on previous research,[25–27] we classified participants into two groups (CCI≥6 and CCI<6).

Table 1. Clinical characteristics of participants

Item	Number
mGPS	
Normal/low-nutrition group	19
Pre-cachexia/refractory cachexia group	116
BI	
≥45 group	37
<45 group	98
CCI	
≥6 group	101
<6 group	34
Primary cancer site	
Breast	13
Other	122

Statistical Analysis

Univariate analysis (Fisher test or Mann–Whitney U test) and logistic regression analysis were performed to identify variables (i.e., sex, age, primary cancer site, cancer cachexia assessment, ADL, and comorbidities) as predictors of 3-month overall survival. Statistical analyses were performed using SPSS version 22.0 (IBM, Tokyo, Japan). $P<0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

The clinical characteristics of the patients are shown in **Table 1**. One hundred and thirty-five consecutive patients (73 men, 62 women) were recruited. The average (±standard deviation) patient age at the time of the study was 74.3±11.2 years.

Cachexia in Palliative Cancer Patients Undergoing Rehabilitation

The prevalence of cancer cachexia among palliative cancer patients undergoing rehabilitation was 4.4% (n=6) in the normal group, 9.6% (n=13) in the low-nutrition group, 9.0% (n=12) in the pre-cachexia group, and 77% (n=104) in the refractory cachexia group. Overall, 116 (86.0%) of the 135 palliative cancer patients were identified as having cachexia.

Factors Affecting Overall Survival

The results of univariate analysis (Fisher and Mann–Whitney U tests) for 90-day survival are shown in **Table 2**. There were 63 patients in the ≥90-day survival group and 73 patients in the <90-day survival group. Significant differences were observed between the 90-day survival groups for mGPS and BI ($P<0.05$).

The variable assignments of multivariate logistic regression are shown in **Table 3**, and the results of the logistic regression analysis for factors predicting overall survival are shown in **Table 4**. mGPS (normal/low-nutrition group) was a positive factor for overall survival at 90 days. Higher ADL was a positive factor for 90 days of overall survival ($P<0.05$).

DISCUSSION

This study examined the prevalence of cachexia in cancer patients at the start of rehabilitation and the factors affecting survival prognosis in the palliative stage. The results showed that the proportion of patients with cachexia was high, and mGPS and ADL strongly influenced the prognosis.

In this study, 9.0% of patients had pre-cachexia, and 77.0% had refractory cachexia, which are higher levels than reported in previous studies. Silva et al.[28] classified advanced cancer patients in palliative care according to mGPS, reporting 3.9% with pre-cachexia and 26.4% with refractory cachexia. In a study of patients with inoperable pancreatic cancer and receiving palliative chemotherapy, Bye et al.[29] reported the prevalence of pre-cachexia and refractory cachexia as 25% and 10%, respectively. Palliative care patients with cancer cachexia have multiple symptoms. It is difficult to provide active interventions to maintain and improve

Table 2. Factors predicting overall survival: univariate analysis

Variable	≥90-day survival	<90-day survival	P value
Sex (male/female)	32/31	41/31	0.494
Age (years)	78 (49–95)	75 (47–93)	0.148
Primary cancer site (breast/other)	5/58	8/64	0.574
mGPS (normal and low-nutrition/pre-cachexia and refractory cachexia)	13/50	6/66	0.049
BI (≥45 group/<45 group)	23/40	14/58	0.034
CCI (≥6 group/<6 group)	48/15	53/19	0.843

Data given as number or median (range).

Table 3. Variable assignments of multivariate logistic regression

Factor	Variable	Assignment
90-day survival	Y	≥90-day survival = 1; <90-day survival = 0
Sex	X_1	Male = 1; female = 0
Age	X_2	Continuous variables
Primary cancer site	X_3	Breast = 1; other = 0
mGPS	X_4	Normal/low nutrition = 1; pre-cachexia/refractory cachexia = 0
BI	X_5	BI ≥ 45 = 1; BI < 45 = 0
CCI	X_6	CCI < 6 = 1; CCI ≥ 6 = 0

Table 4. Factors predicting overall survival: logistic regression analyses

Variable	Odds ratio (95% CI)	P value
Sex	1.269 (0.595–2.708)	0.538
Age	1.027 (0.993–1.063)	0.117
Primary cancer site	0.730 (0.193–2.753)	0.642
mGPS	3.438 (1.118–10.572)	0.031
BI	2.783 (1.218–6.361)	0.015
CCI	1.122 (0.491–2.564)	0.785

CI, confidence interval.

ADL and dyspnea, relieve pain, and improve or maintain quality of life. Cancer cachexia in palliative cancer patients should be diagnosed at the start of rehabilitation using mGPS to allow rehabilitation programs to be designed according to the degree of cancer cachexia.

The results of this study indicate that mGPS significantly reflects prognosis in palliative cancer patients and is an important assessment in determining the physical condition of each patient. The main symptom of cancer cachexia is a decrease in skeletal muscle mass, which is influenced by decreased anti-inflammatory activity caused by cancer tumors and increased inflammation caused by decreased physical activity. In these patients, skeletal muscle anabolic stimulation and anabolic resistance are reduced, and skeletal muscle synthesis declines, leading to a vicious cycle of reduced physical function.[30] The association between mGPS and overall survival has been reported by Silva et al.[28] and Pantano et al.[31] In addition, overall survival is associated with Karnofsky Performance Status in more advanced cancer patients who receive only palliative care. Furthermore, mGPS was significantly associated with lower skeletal muscle radiation intensity, failure in the Timed Up-and-Go test, and failure in the hand grip strength test in patients with advanced cancer.[32]

The progressive decline in ADL in palliative cancer patients leads to decreased physical activity, which reduces the patient's quality of life and affects their survival prognosis. In this study, a decline in ADL was strongly related to survival prognosis.

Palliative cancer patients experience progressive declines in ADL because of loss in skeletal muscle mass associated with worsening general condition and cancer cachexia. In lung cancer patients with cancer cachexia, items on the BI such as stair climbing, bathing, and voiding were observed as early disabling events and shorter asymptomatic survival has been reported.[33] Poor performance status was also significantly associated with low skeletal muscle density, low skeletal muscle, and poor Timed Up-and-Go performance.[32] A systematic review of the effects of exercise therapy on advanced cancer patients at high risk of developing cachexia reported benefits on physical function and fatigue. However, high program dropout rates and low compliance rates were reported as limitations of these studies.[34,35] When implementing rehabilitation for palliative cancer patients, it may be necessary to adjust intervention frequency and exercise load as appropriate to maintain physical activity and ADL.

Our study found no association between comorbidities and survival prognosis. The CCI is a prognostic factor for liver, breast, gastric, pancreatic, and colorectal cancer patients.[36–40] Several studies have reported chronic obstructive pulmonary disease and diabetes mellitus as complications in lung cancer patients and diabetes mellitus as a complication in breast cancer patients.[41,42] Number of comorbidities and CCI score are also reported as significant predictors of survival outcomes in cancer patients.[43–45] This study included multiple cancer types, and 81% of patients had a CCI of 3 or higher. The patients in our study were palliative cancer patients, many of whom had multiple comorbidities. This suggests that the CCI is not a significant predictor of survival.

Study Limitations

There were several limitations in this study. First, the study included patients from a single institution and did not examine patients from other institutions. Second, the measurement items in this study did not include symptoms such as dyspnea and fatigue, nor physical functions such as muscle strength and balance ability, so the effects of these symptoms were not examined. Third, the participants of this study were selected from patients for whom survey data could be extracted, and the study period was short. Further research is needed to examine these issues.

CONCLUSION

In this study of palliative cancer patients undergoing rehabilitation, 86% had cancer cachexia. The mGPS and BI were associated with survival prognosis. Combining mGPS classification and ADL assessment may provide some prognostic information when implementing rehabilitation for palliative cancer patients. The difference in prognosis may influence the design of the rehabilitation content, such as when to prioritize exercise therapy and movement training, when to reduce physical and psychological symptoms, and what patients want to do in their final days.

ACKNOWLEDGMENTS

The authors acknowledge the assistance of the study participants.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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