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The Effect of Cachexia on the Prognosis of Pancreatic Cancer Patients

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Abstract: Purpose: Cachexia is a syndrome characterized by physical wasting owning to reduced food intake and abnormal metabolism. The relationship between cachexia and prognosis of patients with pancreatic cancer remains unclear. This study aimed to elucidate the effect of cachexia on the survival of patients with pancreatic cancer.
Methods: A total of 106 patients with pancreatic cancer were enrolled in this study. We divided the participants into cachexia group and non-cachexia group as per the diagnostic criteria of the European Society for Clinical Nutrition and Metabolism 2010 guidelines. The Kaplan-Meier survival curves between the two groups were compared using the log-rank test, and the Cox proportional hazard model was applied to calculate the hazard ratio (HR) of death caused by pancreatic cancer after adjustment for potential confounding factors.
Results: At the time of cancer diagnosis, the number of cachexic and non-cachexia patients was 29 and 77, respectively. There were significant differences in body weight, body metabolic index, total lymphocyte count, albumin, and cholinesterase between the cachexia and non-cachexia groups. The cachexia group had a shorter survival rate than the non-cachexia group (50% survival time was 295 days and 662 days, respectively), and the survival difference was statistically significant (p=0.001). After adjusting for age, sex, and clinical stage, cachexia still significantly increased the risk of death caused by pancreatic cancer (HR: 1.648; 95% confidence interval: 1.009–2.692).
Conclusions: A significant association was found between cachexia at the time of diagnosis and prognosis in patients with pancreatic cancer. This finding indicates that cachexia at diagnosis is a useful prognostic factor in patients with pancreatic cancer.

Key Words: cachexia, pancreatic cancer, prognostic factor

Introduction

Pancreatic cancer remains one of the malignancies with the worst prognosis, with an average 5-year survival rate of 4–6% (1). With the development of novel chemotherapeutic agents and surgical techniques, the prognosis of patients with pancreatic cancer has improved over the past decade. Although clinicopathologic factors, such as lymphovascular invasion, which determine the success of surgical management and R0 resection margin, have been explored extensively, additional prognostic variables must be explored for further improvement of patient outcomes (2-8).

One common symptomatic presentation of cancer patients is cachexia, which is often highlighted by weight loss. Accumulating evidence suggests that the symptoms of cachexia represent independent prognostic factors that determine patient survival (9). Malignant neoplasms release cytokines that alter metabolism, which causes destruction or wasting of the muscle and adipose tissue, leading to cachexia (10-13). Serum markers that determine cachexia are adiponectin, ghrelin, and leptin, among others (14). However, these tests are limited to academic settings and not conducive for clinical use. In recent years, nutritional management of cancer patients, especially protein intake, has gained increasing attention (15).

Despite the increasing number of studies focusing on the nutritional management of cancer patients, the relationship between cachexia and prognosis of

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pancreatic cancer remains unclear (16). In this study, we aimed to discover new prognostic factors and the effect of cachexia on the survival rates of patients with pancreatic cancer.

Study design and Methods

Participants

Initially, 114 patients with pancreatic cancer who were admitted to the Department of General and Digestive Surgery, Kanazawa Medical University Hospital were included in this study. These patients were diagnosed with pancreatic cancer between January 2009 and February 2019. Of these, two patients who died during the perioperative period, and a total of six cases of mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN) were excluded (Figure 1). Therefore, this study was conducted on 106 patients.

Definition and criteria for the diagnosis of cachexia

The diagnostic criteria for cachexia in this study were based on the 2010 guidelines of the European Society for Clinical Nutrition and Metabolism (17). In this criteria, cachexia is defined as weight loss greater than 5% in the past 6 months or as body mass index (BMI) less than 20 kg/m^2, and weight loss greater than 2% or sarcopenia and weight loss greater than 2%. In addition, supplementary criteria that include interleukin-6 (IL-6) >4 pg/dL, C-reactive protein (CRP) >0.5 mg/dL, hemoglobin (Hb) <12 g/dL, and serum albumin (Alb) <3.2 g/dL, define cachexia in patients who do not meet the weight-loss based criteria (13, 15, 18-20) because cachexia is clinically characterized by poor oral intake and inflammation.

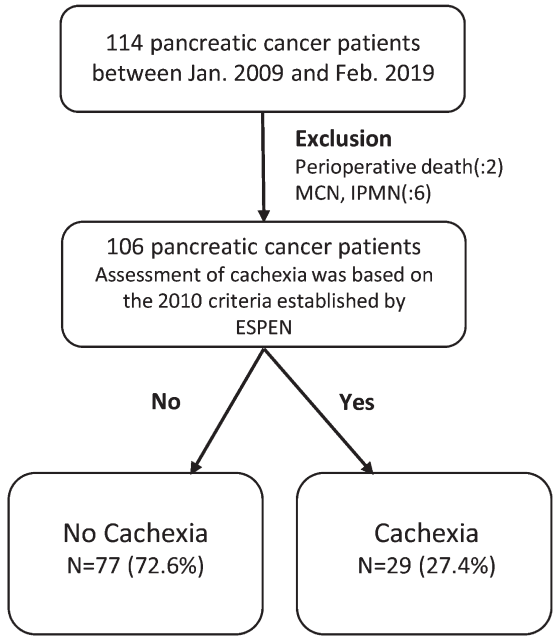

Figure 1. Flow diagram of the pancreatic cancer patients used for survival analysis.

Data collection and follow-up

We collected information regarding the clinical and pathological examinations at diagnosis, initial treatment, and follow-up visits until October 2020 in the study participants. Sarcopenia was simply evaluated using computed tomography (CT). The total cross sectional area of the psoas major muscle mass at the third lumbar (L3) level was measured using the manual trace method, then the psoas major muscle index (cut-off value: male patients, 6.36 cm^2/m^2; female patients, 3.92 cm^2/m^2) was calculated to determine the presence of sarcopenia (21). The participants were observed from the date of diagnosis to death caused by pancreatic cancer, death from any other cause, or last follow-up visit.

Statistical analyses

We compared the characteristics and treatment of study participants between the cachexia and non-cachexia groups. Pancreatic cancer-specific survival rate was calculated in each group using the Kaplan-Meier method, and the log-rank test was used to evaluate the statistical differences in the observed survival curves. The Cox proportional hazard model was applied for univariate and multivariate survival analysis to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) of death caused by pancreatic cancer. In multivariate analysis, age, sex, and clinical stage were included in the model to adjust for potential confounding factors. Statistical significance was defined as $p<0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences® [SPSS] software version 20.0 (SPSS Inc., Chicago, IL).

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki. A written informed consent was obtained from all the patients. The study protocol was reviewed and approved by the Ethics Board of the Kanazawa Medical University Hospital (No. I-132). All samples were anonymized before analysis to guarantee and protect privacy.

Results

Of the 106 patients with pancreatic cancer in this study, the number of cachexic and non-cachexic patients was 29 and 77, respectively (Figure 1). In the cachexia group, 20 patients displayed weight loss greater than 5%, and eight patients with BMI less than 20 kg/m^2 showed weight loss greater than 2%. In addition, one

patient who did not meet weight-loss based criteria was classified into the cachexia group based on the supplementary criteria described in the study design and method section. CT at the time of diagnosis of pancreatic cancer showed that none of the other cases corresponded to sarcopenia. Therefore, no patient was categorized into the cachexia group based on the existence of sarcopenia and weight loss greater than 2%.

The treatment modalities of the study participants were as follows: 43 resection (three total pancreatectomy, 17 pancreaticoduodenectomy, and 23 distal pancreatectomy), 48 radiation therapy (two radiation alone, two combined with surgery, 18 surgery and chemotherapy, and 26 chemo-radiotherapy), 92 chemotherapy (28 chemotherapy alone, 18 surgery and radiotherapy, 20 combined with surgery, and 26 combined with radiotherapy), and eight palliative care.

Table 1 presents the characteristics and treatment of patients with and without cachexia. There were significant differences in body weight, BMI, total

Table 1. Comparison of patient characteristics between cachexic and non-cachexic groups.

Patients characteristics	No Cachectic (*n*=77)	Cachectic (*n*=29)	*p* value
Sex (% male)	43 (56.0)	14 (48.0)	0.519[b]
Age (mean±SD)	69.7 ± 8.6	70.4 ± 11.5	0.747[c]
Weight (＜54.1[a] kg) (%)	32 (44.6)	21 (72.4)	0.004[b]
BMI (mean±SD)	22.5 ± 3.0	19.5 ± 2.6	<0.001[d]
% Weight loss median (range)	1.2 (-8.7～4.9)	6.9 (-1～22.6)	<0.001[e]
ECOG PS			0.105[f]
0 (%)	53 (68.8)	16 (55.2)	
1 (%)	21 (27.3)	8 (27.6)	
2 (%)	21 (27.3)	4 (13.8)	
3 (%)	1 (1.3)	1 (3.5)	
History of diabetes (%)	47 (61.0)	18 (62.1)	1.00[b]
TLC (＜1350[a] /μL) (%)	31 (40.3)	21 (72.4)	0.003[b]
CRP (≧1.0mg/dL) (%)	16 (20.8)	11 (37.9)	0.084[b]
Alb (＜4.0[a] g/dL) (%)	27 (35.1)	17 (58.6)	0.025[b]
ChE (＜214[a] U/L) (%)	29 (37.7)	23 (79.3)	<0.001[b]
Clinical Stage			0.003[f]
I (%)	12 (15.6)	3 (10.3)	
II (%)	30 (39.0)	5 (17.2)	
III (%)	24 (31.2)	8 (27.6)	
IV (%)	11 (14.3)	13 (44.8)	
Resection (%)	37 (48.1)	6 (21.4)	0.014[b]
Surgery TP (%)	2 (5.4)	1 (16.7)	
PD (%)	15 (40.5)	2 (33.3)	
DP (%)	20 (54.1)	3 (50.0)	
Radiotherapy (%)	37 (48.1)	11 (39.3)	0.388[b]
Chemotherapy (%)	67 (87.0)	25 (86.0)	0.830[b]
GEM (%)	22 (32.8)	11 (44.0)	
S-1 (%)	21 (31.3)	10 (40.0)	
GEM + nab-PTX (%)	15 (19.5)	3 (12.0)	
GEM + S-1 (%)	8 (11.9)	1 (4.0)	
FORFIRINOX (%)	1 (1.4)	0 (0)	

[a] median, [b] Fisher's exact test, [c] Welch's t-test, [d] Student t-test, [e] Mann-Whitney U-test, [f] Pearson's chi-square test, BMI; body mass index, SD; standard deviation, ECOG PS; Eastern Cooperative Oncology Group Performance Status, TLC; total lymphocyte count, CRP; C-reactive protein, Alb; albumin, ChE; cholinesterase, TP; total pancreatectomy, PD; pancreaticoduodenectomy, DP; distal pancreatectomy, GEM; gemcitabine, S-1; tegafur, gimeracil, and oteracil, nab-PTX; nab-paclitaxel, FOLFIRINOX; leucovorin, fluorouracil, irinotecan, and oxaliplatin

lymphocyte count (TLC), Alb, and cholinesterase levels between the two groups. In addition, the proportion of patients in advanced clinical stages was higher in the cachexia group, and the proportion of patients with surgical treatment was more common in the non-cachexia group. The proportion of patients with high CRP levels was higher in the cachexia group, and the difference was marginally significant (p=0.084). The differences in sex, age, Eastern Cooperative Oncology Group Performance Status (ECOG PS) and history of diabetes were not significant.

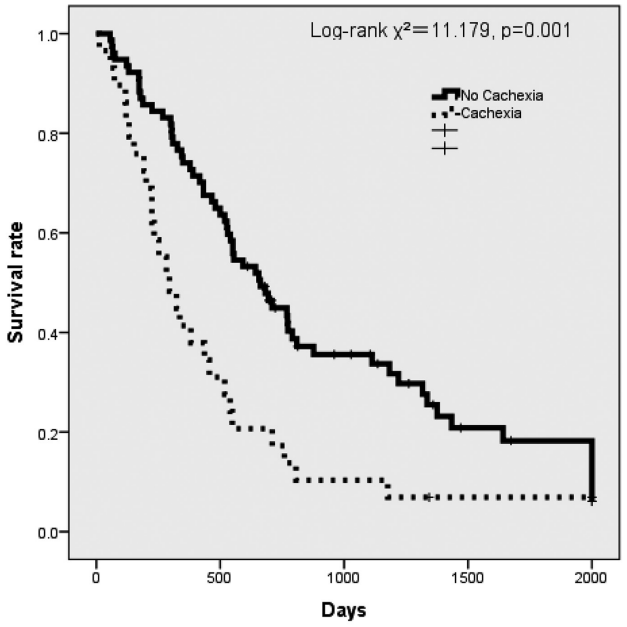

Figure 2. Kaplan-Meier curve illustrating survival differences based on the presence of cachexia at the time of cancer diagnosis.

As shown in Figure 2, patients with cachexia had lower survival rates than those without cachexia (50% survival time 295 days and 662 days, respectively), and the survival difference was statistically significant (p=0.001). Table 2 shows the results of univariate and multivariate analyses using the Cox model. The existence of cachexia was significantly associated with an increased risk of death caused by pancreatic cancer in the univariate analysis (HR: 2.128; 95% CI: 1.367–3.479). In the multivariate analysis, patients with cachexia showed worse prognosis after adjustment for age, sex, and clinical stage, and the hazard ratio was statistically significant (HR: 1.648; 95% CI: 1.009–2.692).

Discussion

Multiple studies have reported the prognostic significance of secondary sarcopenia, which is a combined manifestation of poor oral intake, underlying inflammation, and protein dysfunction in cancer patients (22, 23). To the best of our knowledge, no study has focused on the relationship between the presence of cachexia at the time of diagnosis and the prognosis of pancreatic cancer, and consensus has not been reached. In this study, 27.4% of patients demonstrated cachexia at the time of initial cancer diagnosis. We found that the presence of cachexia negatively affected the survival rate.

The nutritional and physical status of cancer patients are determined by two distinct variables: cancer-associated weight loss and cancer-driven weight loss (24). Cancer-associated weight loss is characterized by decreased gastrointestinal absorption and oral intake. This process is reversible. However, cancer-driven weight loss is caused by host-tumor interaction, whose primary manifestation is cachexia.

Table 2. Univariate and multivariate survival analyses by the Cox model, cachexia in patients with pancreatic cancer.

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Cachexia (present)	2.128	1.367 - 3.479	0.002	1.648	1.009 - 2.692	0.046
Sex (female)	1.278	0.856 - 2.045	0.263	1.366	0.876 - 2.133	0.169
Age (≥70)	1.481	1.149 - 2.856	0.080	2.155	1.363 - 3.409	0.001
Clinical Stage I	1.0			1.0		
II	1.311	0.589 - 2.914	0.507	1.354	0.637 - 3.020	0.459
III	1.954	0.888 - 4.303	0.096	2.177	0.979 - 4.884	0.057
IV	10.453	4.457 - 24.51	<0.001	14.045	5.722 - 34.478	<0.001

HR; hazard ratio, 95%CI; 95% confidence interval

This process is considered irreversible. These facts indicate that controlling cancer-driven weight loss is critical for prolonging patient survival.

At the time of initial diagnosis, the majority of pancreatic cancer patients showed significant biliary inflammation, obstructive pancreatitis, and an overall decrease in secretory functions. During treatment, many patients showed weight loss and decreased serum Alb levels owning to chemoradiation. We hypothesize that the above changes are manifestations of cancer-associated weight loss, which is still reversible. As these patients experience metastasis and recurrence, the predominant process shifts to cancer-driven weight loss. At this stage, patients experience global metabolic dysfunction, characterized by decreased serum Alb levels and cachexia. In summary, the manifestation of weight loss is driven not only by a process, but also by a spectrum that consists of two biochemical processes. The ratio of cancer-associated and driven processes differs depending on the stage of disease progression.

Studies have shown that the release of cytokines by malignant neoplasms causes metabolic dysfunction and drives muscle wasting and subsequent weight loss, leading to cachexia (12, 23). Cachexia is the predominant manifestation of cancer-driven weight loss. It is a biological process characterized by global metabolic dysfunction, which undergoes dynamic changes throughout the course of the disease. In postoperative states or with significant disease burden, decreased amounts of type II muscle fibers, myosin, and excitatory muscle activity are often seen (25, 26). A combination of nutritional support and physical activity has proven effective in acute care settings. It has been proposed that multidisciplinary strategies, such as the ABCDE bundle, which encourages optimal feeding with adequate protein intake and muscle-strengthening activities need to be increases (27-30).

At the time of diagnosis in patients with pancreatic cancer, assessment of cachexia is a useful measure for improvement of the prognosis because early intervention to improve nutritional status for patients with cachexia is considered to increase the number of patients who can undergo curative surgical resection.

There may be some possible limitations of this study. First, patients' weight changes over the past 6 months were assessed by self-reports, which may lead to misclassification of cachexia in some patients. Second, we did not measure serum markers of cachexia, such as adiponectin, ghrelin, and leptin. Therefore, we could not evaluate the effects of these markers on pancreatic cancer patients with cachexia. Third, the limited number of cases in this study inhibited detailed investigation, including stratified analysis by clinical stage.

Conclusions

Cachexia at the time of cancer diagnosis was found to have a significant effect on the prognosis of patients with pancreatic cancer after adjusting for potential confounding factors. This finding indicates that the presence of cachexia at the time of diagnosis is a useful prognostic factor in patients with pancreatic cancer. Nutritional management is important for pancreatic cancer patients with cachexia at diagnosis to enable curative surgical resection.

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Patient Consent for Publication

Not applicable.

Conflict of interest

The author declares no conflict of interest.

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