Effect of pretreatment psoas muscle mass on survival for patients with unresectable pancreatic cancer undergoing systemic chemotherapy

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Received January 13, 2017; Accepted April 4, 2017

DOI: 10.3892/ol.2017.6952

Abstract. To the best of our knowledge, there are few previous studies that have investigated the effect of decreased skeletal muscle mass (DSMM) on survival in patients with unresectable advanced pancreatic cancer (APC) who are undergoing systemic chemotherapy. Thus, the present study aimed to investigate the impact of DSMM, as determined by the psoas muscle index (PMI) following computed tomography and prior to systemic chemotherapy, on the outcomes of patients with unresectable APC (n=61). The primary endpoint used was the overall survival (OS) rate. The OS rates in the PMI-High group (exceeds the median PMI value in each gender) were retrospectively compared with those in the PMI-Low group (below the median PMI value in each gender), and factors associated with OS were investigated using univariate and multivariate analyses. The study cohort included 31 male and 30 female patients with a median age of 72 years, 13 of whom were stage IVA, and 48 were stage IVB. The median PMI in males was 4.3 cm^2/m^2 (range, 1.6-8.2 cm^2/m^2), while that in females was 2.3 cm^2/m^2 (range, 0.7-6.1 cm^2/m^2). The proportion of patients with performance status 0 in the PMI-High group was significantly high, compared with that in the PMI-Low group [83.3% (25/30) vs. 58.1% (18/31); P=0.0486]. Body mass index in the PMI-High group was significantly higher compared with that in the PMI-Low group (P=0.0154). The 1-year cumulative survival rate was 43.3% in the PMI-High group and 12.9% in the PMI-Low group (P=0.0027). Following multivariate analysis, PMI (P=0.0036), prothrombin time (P=0.0044) and carbohydrate antigen 19-9 (P=0.0451) were identified to be significant predictors of OS. In conclusion, DSMM, as determined by the PMI, could be a significant predictor of prognosis in patients with unresectable APC who are receiving systemic chemotherapy.

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Abbreviations: APC, advanced pancreatic cancer; DSMM, decreased skeletal muscle mass; UICC, Union for International Cancer Control; CT, computed tomography; EUS, endoscopic ultrasonography; PS, performance status; ECOG, Eastern Cooperative Oncology Group; L3, the third lumber; PMI, psoas muscle index; H, high; L, low; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CTCAE, Common Terminology Criteria for Adverse Events; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; SAE, serious adverse event; NE, not evaluated; PT, prothrombin time; CRP, C reactive protein

Key words: unresectable advanced pancreatic cancer, systemic chemotherapy, psoas muscle index, prognosis

Introduction

The pancreas serves an essential role in the digestive system, including producing numerous digestive enzymes (1-3). In 2013, pancreatic cancer (PC) was reported to be the fourth leading cause of cancer-associated mortality worldwide (4). The majority of patients with PC present with locally advanced or metastatic disease at initial diagnosis and the proportion of patients who can proceed with curative intent surgery is <20% (1,3). Patients with advanced (A)PC have a poor prognosis (5-9). Among patients with metastatic PC, the 5-year survival rate is reported to be ~2% (10). Current Japanese guidelines for systemic chemotherapy in patients with APC recommend the use of gemcitabine monotherapy, S-1 monotherapy, gemcitabine and S-1 combination therapy, nab-paclitaxel and gemcitabine combination therapy, or a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil and leucovorin, based on the baseline and tumor status of each patient (5-8).

Skeletal muscle is considered to be a large endocrine organ, which accounts for ~50% of an individual's body weight and possesses the capacity for high metabolic activity (11). In general, skeletal muscle mass is regulated depending on the balance between protein synthesis and protein catabolism (12). Sarcopenia, defined as decreased skeletal muscle mass (DSMM) and muscle strength, has become a relevant clinical feature for understanding the effects of aging on clinical outcomes (13). Sarcopenia is a commonly observed disorder in aged populations and is associated with disability, functional decline and frailty (13,14). Age-associated sarcopenia is defined as primary sarcopenia, whilst advanced malignancies, as well as chronic inflammatory diseases including renal, heart and liver diseases, can be the causes of secondary sarcopenia (12-16). Severe underlying diseases can lead to sarcopenia and cachexia, which involves body weight loss and muscle wasting. Furthermore, substantial skeletal muscle wasting is an important predictor in patients with solid malignancies, although the precise mechanisms by which DSMM increases the risk of mortality remain unclear (17,18). Knowledge of the underlying mechanisms in advanced malignancies associated with skeletal muscle wasting may lead to the development of novel therapeutic drugs. Thus, in recent years, this clinical area has attracted much attention among oncologists.

A number of studies have demonstrated that DSMM could be an adverse predictor for patients with PC who were treated with surgical resection (16,19-23). However, to the best of our knowledge, there are few reports regarding the impact of DSMM on survival in patients with unresectable APC undergoing systemic chemotherapy (24,25). Therefore, it is imperative to address these issues. Thus, the aims of the present study were to investigate the impact of DSMM prior to systemic chemotherapy on the clinical outcomes of patients with unresectable APC.

Patients and methods

Patients and indications for systemic chemotherapy. Between February 2008 and November 2015, 80 consecutive patients diagnosed with unresectable APC undergoing systemic chemotherapy were admitted to Hyogo College of Medicine (Nishinomiya, Hyogo, Japan). There were 31 male and 30 female patients with a median age of 72 years (range, 39-89). All patients were treatment naive for APC. Cases with distal common bile duct cancer, ampulla of Vater carcinoma or neuroendocrine carcinoma of the pancreas were excluded. Of these, 19 patients with unknown clinical outcomes (succumbed to disease or surviving) due to loss of follow-up were excluded from the current analysis. Thus, a total of 61 patients with APC who underwent systemic chemotherapy were analyzed in the present study. Clinical stage for APC was determined based on Union for International Cancer Control (UICC) classification system (26). In cases with local APC without distant metastases, indication for surgery was reviewed in each case through discussion with oncologists and surgeons (27-31). In principal, systemic chemotherapy was recommended for patients with PC with the following characteristics, as determined by radiological findings: Dynamic computed tomography (CT), magnetic resonance imaging and endoscopic ultrasonography (EUS). This was following informed consent from each patient. The presence of distant metastases and/or the presence of tumor vascular invasion was judged as unresectable PC. Patients with poor performance status [PS; Eastern Cooperative Oncology Group (ECOG) classification ≥3] were not recommended for systemic chemotherapy (32). The presence of ascites was not contraindicated for systemic chemotherapy.

Definition of DSMM and the study protocol. Assessment of muscle mass was performed using CT scans obtained prior to systemic chemotherapy. The third lumber (L3) level was selected as a standard. Bilateral psoas muscles at the L3 level were identified on the CT images. Cross-sectional areas (cm^2) of these muscles were measured by manual tracing on the CT images, and their sum was calculated. These sums were normalized for each patient to provide a psoas muscle index value (PMI; cm^2/m^2) (33,34). The median PMI value was calculated for males and females separately. Patients with a PMI of more than each median value were defined as the PMI-High (H) group and those with a PMI of less than each median value as the PMI-Low (L) group. This is due to the optimal cut-off point of PMI for DSMM in Japanese patients with PC having not yet been well established.

The primary endpoint was overall survival (OS) in the present study. Baseline characteristics and OS in the PMI-H and PMI-L groups were retrospectively compared, and factors associated with OS were investigated using univariate and multivariate analyses. The current study was performed in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Hyogo College of Medicine (approval no. 2117).

Diagnosis for pancreatic cancer and systemic chemotherapy. PC was diagnosed primarily based on the current guidelines (35). Briefly, abdominal US and dynamic CT of the pancreas was routinely performed prior to initiating systemic chemotherapy (33). In cases with atypical radiological findings for PC, tumor biopsy or EUS-guided fine needle aspiration was considered (36). In the present study, the pathological diagnosis was confirmed in 15 cases (24.6%).

The selection of chemotherapeutic agents was determined by each attending physician. For patients with no evident risk factors, the recommended initial dosage of each chemotherapeutic agent (gemcitabine, S-1, nab-paclitaxel, and 5-fluorouracil) was administered (5,37). The reduced initial dosage was administered to certain patients based on clinical features, including age, body weight, ECOG-PS and laboratory data. During systemic chemotherapy, each attending physician adjusted the dosage of chemotherapeutic agents according to the grade of adverse events. In patients with adverse events, systemic chemotherapy was discontinued until the clinical symptoms resolved to grade 1 or 2, and other alternative chemotherapeutic regimens were considered. In patients with poor response to initial chemotherapy, other alternative chemotherapeutic regimens were also considered.

In principle, the treatment efficacy for systemic chemotherapy was assessed every 2-4 months following the initiation of chemotherapy, according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) using radiological findings and/or the levels of various tumor markers, including

carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 (38). Patients continued systemic chemotherapy until the development of any of the following conditions: Unacceptable drug toxicity, tumor progression or the patient's request to stop treatment. Chemotherapy-associated adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE; version 3.0) (39).

Evaluation of treatment response during chemotherapy. The most improved treatment response achieved during chemotherapy was determined according to the RECIST criteria (version 1.1), as previously described (7,38). The most improved treatment response was graded using the following four categories: (1) Complete response (CR); (2) partial response (PR); (3) stable disease (SD); (4) progressive disease (PD) (38). The objective response rate (ORR) was defined as the proportion of patients with the most improved treatment response rates when considering CR and PR. The disease control rate (DCR) was defined as the proportion of patients with the most improved treatment response rates when considering CR, PR and SD.

Statistical analysis. The categorical parameters in the PMI-H and PMI-L groups were analyzed using Fisher's exact test, while the numerical parameters were analyzed either with an unpaired Student's t-test or with a Mann-Whitney U test as appropriate. OS curves were created using the Kaplan-Meier estimator method and compared using the log-rank test. Variables that were considered significant following univariate analysis were entered into the multivariate analysis with Cox's proportional hazards model. For the purpose of analyzing the significance of predictors in multivariate analyses, analyzed variables were divided by the median values for all cases (n=61) and treated as dichotomous covariates. OS was defined as the time interval from the initiation of systemic chemotherapy until mortality (due to any cause) or to the final follow-up visit. Data are presented as the median values (range) unless otherwise stated. $P<0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using JMP software (version 11.0; SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics. The baseline characteristics of the analyzed patient cohort (n=61) are presented in Table I. Of these, 13 were stage IVA and 48 were stage IVB, as determined using the UICC classification system. Maximum tumor size in patients ranged between 1.4 and 9.4 cm (median, 3.6 cm). The median PMI in males was 4.3 cm^2/m^2 (range, 1.6-8.2 cm^2/m^2), whereas in females it was 2.3 cm^2/m^2 (range, 0.7-6.1 cm^2/m^2). Patients were predominantly PS-0 (70.5%; 43/61). As for initial chemotherapeutic regimens, gemcitabine monotherapy was performed in 44 patients, S-1 monotherapy in 10, gemcitabine and S-1 combination therapy in 5, nab-paclitaxel and gemcitabine combination therapy in 1, and 5-fluorouracil monotherapy in 1.

Comparison of baseline characteristics between the PMI-H and the PMI-L group. The proportion of patients with PS-0 in the PMI-H group was significantly higher compared with that in the PMI-L group [83.3% (25/30) vs. 58.1% (18/31); P=0.0486]. Body mass index (BMI) in the PMI-H group was significantly higher compared with that in the PMI-L group (P=0.0154). As for other baseline characteristics, no significant differences were identified between the two groups (Table II).

Table I. Baseline characteristics of patients with unresectable advanced pancreatic cancer undergoing systemic chemotherapy (n=61).

Variable	Value (range)
Age, years	72 (39-89)
Gender, male/female	31/30
ECOG-performance status, 0/1/2	43/15/3
Psoas muscle index, cm^2/m^2, male	4.3 (1.6-8.2)
Psoas muscle index, cm^2/m^2, female	2.3 (0.7-6.1)
Body mass index, kg/m^2	21.2 (15.1-31.6)
Pancreatic cancer stage, IVA/IVB	13/48
Maximum tumor size, cm	3.6 (1.4-9.4)
Primary site, uncus or head/body or tail	33/28
Total bilirubin, mg/dl	0.7 (0.3-6.6)
Serum albumin, g/dl	3.5 (1.8-4.4)
Prothrombin time, %	86.3 (47.5-127)
Platelet count, $x10^4/mm^3$	20.8 (7.1-45.9)
White blood cell, $x10^3/\mu l$	6.05 (2.54-29.76)
Hemoglobin, g/dl	11.6 (7.5-15.7)
Serum creatinine, mg/dl	0.65 (0.28-7.41)
C reactive protein, mg/dl	0.6 (0-22.0)
AST, IU/l	26 (11-265)
ALT, IU/l	30 (8-289)
ALP, IU/l	361 (139-1929)
GGT, IU/l	98 (11-747)
Amylase, IU/l	66 (7-357)
CEA, IU/l[a]	3.95 (1.4-286.1)
CA19-9, IU/l	408 (0.6-42414)

Data are presented as the number of patients or the median (range). [a]Missing data, n=3. ECOG, the Eastern Cooperative Oncology Group; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transpeptidase; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Cumulative OS rates for all cases and comparison of OS rates between the PMI-H and the PMI-L group. The median follow-up period following initial systemic chemotherapy for all cases was 246 days (range, 25-1,304 days). For all cases, the 6 month, 1- and 2-year cumulative survival rates were 59.0, 27.9 and 9.1%, respectively (Fig. 1). The median follow-up period following initial systemic chemotherapy was 357 days (range, 25-1,304 days) in the PMI-H group and 155 days (range, 26-900 days) in the PMI-L group. The 6 month, 1- and 2-year cumulative survival rates were 73.3, 43.3 and 15.2%, respectively, in the PMI-H group, and 45.2, 12.9 and 3.2%, respectively, in the PMI-L group (P=0.0027; Fig. 2).

Table II. Comparison of baseline characteristics between the PMI-H and the PMI-L group.

Variables	Value (range)		P-value
	PMI-H	PMI-L	
Age, years	70 (39-89)	73 (48-88)	0.1350
Sex, male/female	15/15	15/16	1.0000
ECOG-performance status, 0/1/2	25/5	18/13	0.0486
Body mass index, kg/m^2	21.6 (17.3-31.6)	19.9 (15.1-24.8)	0.0154
Pancreatic cancer stage, IVA/IVB	9/21	4/27	0.1271
Maximum tumor size, cm	2.95 (1.4-9.4)	3.8 (2.2-7.6)	0.1635
Primary site, uncus or head/body or tail	16/14	17/14	1.0000
Best treatment response, CR/PR/SD/PD/NE	0/4/12/11/3	0/3/8/13/7	ORR, 0.7072/DCR, 0.2016
Total bilirubin, mg/dl	0.7 (0.3-1.8)	0.8 (0.3-6.6)	0.7062
Serum albumin, g/dl	3.6 (1.8-4.4)	3.4 (2.5-4.4)	0.2806
Prothrombin time, %	86.15 (43.5-109.8)	86.5 (64.7-127)	0.5345
Platelet count, x10^4/mm^3	21.4 (9.1-45.9)	19.5 (7.1-35.3)	0.3124
White blood cell, x10^3/μl	5.92 (3.36-12.75)	6.34 (2.54-29.76)	0.5836
Hemoglobin, g/dl	12.0 (7.6-15.1)	11.5 (7.5-15.7)	0.5342
Serum creatinine, mg/dl	0.64 (0.33-1.28)	0.65 (0.28-7.41)	0.8062
C reactive protein, mg/dl	0.4 (0-22.0)	0.9 (0-6.9)	0.3041
AST, IU/l	31.5 (11-265)	25 (12-124)	0.7127
ALT, IU/l	34 (8-289)	29 (8-109)	0.6084
ALP, IU/l	387.5 (153-1358)	338.5 (139-1929)	0.7096
GGT, IU/l	90.5 (14-747)	98 (11-467)	0.8140
Amylase, IU/l	66 (7-201)	67 (17-357)	0.5255
CEA, IU/l	3.2 (1.5-96.2)	4.1 (1.4-286.1)	0.1591
CA19-9, IU/l	286.4 (0.6-42414)	801.7 (0.6-31020)	0.2741

Data are presented as the number of patients or the median (range). PMI, psoas muscle index; H, high; L, low; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; ORR, objective response rate; DCR, disease control rate; ECOG, the Eastern Cooperative Oncology Group; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transpeptidase; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

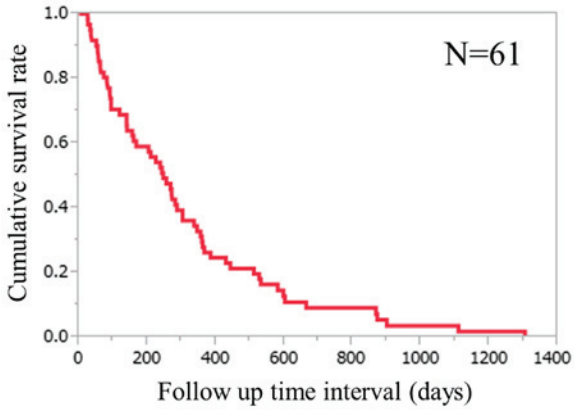

Figure 1. Cumulative overall survival rate for all patients with unresectable advanced pancreatic cancer undergoing systemic chemotherapy (n=61). The 6-month, 1- and 2-year cumulative survival rates were 59.0, 27.9 and 9.1%, respectively.

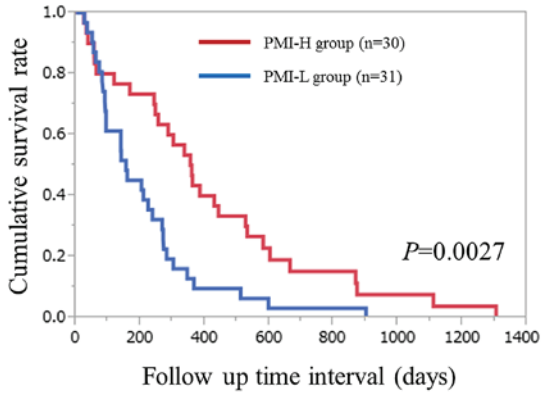

Figure 2. Cumulative overall survival rates for patients with unresectable advanced pancreatic cancer undergoing systemic chemotherapy in each of the PMI-H and PMI-L groups. The 6-month, 1- and 2-year cumulative survival rates were 73.3, 43.3 and 15.2%, respectively, in the PMI-H group, and 45.2, 12.9, and 3.2%, respectively, in the PMI-L group (P=0.0027). PMI, psoas muscle index; H, high; L, low.

Comparison of serious adverse events (SAEs) of grade ≥3 between the PMI-H and the PMI-L groups. The prevalence of chemotherapy-associated SAEs of grade ≥3, as assessed using CTCAE (version 3.0), were 10.0% (3/30) in the PMI-H group and 25.8% (8/31) in the PMI-L group (P=0.1822; data not

Table III. Univariate and multivariate analyses of factors associated with overall survival for patients with unresectable advanced pancreatic cancer (n=61).

			Multivariate analysis		
Variables	No. of patients	Univariate analysis	Hazard ratio	95% CI	P-value
Age, >72/≤72 years	29/32	0.4593			
Sex, male/female	31/30	0.3967			
ECOG-performance status, 0-1/2	43/18	0.6853			
PMI, high/low	30/31	0.0027	2.446	1.340-4.541	0.0036[a]
Body mass index, >21.2/≤21.2 kg/m^2	30/31	0.5700			
Pancreatic cancer stage, IVA/IVB	13/48	0.0026	2.147	0.934-5.207	0.0725
Maximum tumor size, >3.6/≤3.6 cm	29/32	0.0262	0.901	0.489-1.648	0.7351
Primary site, uncus or head/body or tail	33/28	0.1758			
Total bilirubin, >0.7/≤0.7 mg/dl	29/32	0.3342			
Serum albumin, >3.5/≤3.5 g/dl	28/33	0.2986			
Prothrombin time, >86.3/≤86.3%	30/31	0.0052	2.219	1.283-3.874	0.0044[a]
Platelet count, >20.8/≤20.8 x10^4/mm^3	30/31	0.0951			
WBC, >6.05/≤6.05x10^3/μl	30/31	0.4832			
Hemoglobin, >11.6/≤11.6 g/dl	30//31	0.4077			
Serum creatinine, >0.65/≤0.65 mg/dl	28/33	0.6884			
CRP, >0.6/≤0.6 mg/dl	30/31	0.0445	0.665	0.384-1.156	0.1474
AST, >26/≤26 IU/l	29/32	0.9588			
ALT, >30/≤30 IU/l	30/31	0.1678			
ALP, >361/≤361 IU/l	29/32	0.5993			
GGT, >98/≤98 IU/l	30/31	0.0175	0.808	0.425-1.509	0.5053
Amylase, >66/≤66 IU/l	29/32	0.7084			
CEA, >3.95/≤3.95 IU/l	29/29	0.1372			
CA19-9, >408/≤408 IU/l	30/31	0.0008	0.504	0.251-0.985	0.0451[a]

[a]P<0.05. ECOG, the Eastern Cooperative Oncology Group; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transpeptidase; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; HR, hazard ratio; WBC, white blood cell; CRP, C reactive protein; PMI, psoas muscle index.

presented). In the PMI-H group, SAEs of grade ≥3 included severe vomiting (1 patient), severe neuropathy (1 patient) and neutropenia (1 patient). In the PMI-L group, SAEs of grade ≥3 included interstitial pneumonia (1 patient), severe anemia (1 patient), thrombocytopenia (2 patients), liver injury (1 patient), neutropenia (1 patient) and jaundice (2 patients). In the present study, chemotherapy-associated mortality was not observed (data not presented).

Most improved tumor treatment response during chemotherapy. With regard to the most improved treatment response during chemotherapy, out of all cases CR was achieved in 0, PR in 7, SD in 20, PD in 24 and not evaluated (NE) in 10 patients (Table II). The ORR and DCR were calculated to be 11.5% (7/61) and 44.3% (27/61), respectively. In the analysis of the most improved tumor response in the PMI-H group, CR was achieved in 0, PR in 4, SD in 12, PD in 11 and NE in 3 patients. The ORR and DCR were calculated to be 13.3% (4/30) and 53.3% (16/30), respectively. In the analysis of the most improved tumor response in the PMI-L group, CR was achieved in 0, PR in 3, SD in 8, PD in 13 and NE in 7 patients. The ORR and DCR were calculated to be 9.7% (3/31) and 35.5% (11/31), respectively. No significant differences in the most improved treatment response were identified between the PMI-H and PMI-L groups (ORR, P=0.7072; DCR, P=0.2016; Table II).

Causes of mortality. During the follow-up period, 60 patients (98.4%) succumbed to disease. In the PMI-H group, 29 (96.7%) patients succumbed during the follow-up period. All patients succumbed due to tumor progression. In the PMI-L group, 31 (100%) patients succumbed during the follow-up period. All patients succumbed due to tumor progression.

Univariate and multivariate analyses of parameters contributing to OS. The univariate analysis identified that the following factors significantly contributed to OS for all cases (n=61): PMI (H or L; P=0.0027); tumor stage (IVA or IVB; P=0.0026); maximum tumor size (>3.6 cm or ≤3.6 cm P=0.0262); prothrombin time (PT; >86.3% or ≤86.3%; P=0.0052); C reactive protein (CRP; >0.6 mg/dl or ≤0.6 mg/dl; P=0.0445); gamma glutamyl transpeptidase (>98 IU/l or ≤98 IU/l; P=0.0175); CA 19-9 >408 IU/l or ≤408 IU/l (P=0.0008) (Table III). The hazard ratios and 95% confidence intervals determined by multivariate analysis for the 7 variables (selected based on a P<0.05 in

univariate analysis) are detailed in Table III. On multivariate analysis, PMI (H or L; P=0.0036), PT (>86.3% or ≤86.3%; P=0.0044) and CA19-9 (>408 IU/l or ≤408 IU/l; P=0.0451) were identified as significant predictors of OS.

Discussion

The effect of muscle mass depletion on clinical outcomes in solid malignancies is a relevant topic among oncologists (17,18). However, as aforementioned, few reports have addressed this important clinical question in patients with unresectable APC who are receiving systemic chemotherapy (24,25). The present study was, therefore, conducted. The data of the present study revealed that subjects in the PMI-H group survived significantly longer compared with those in the PMI-L group (P=0.0027) and additionally, lower PMI was revealed to be an independent adverse predictor for survival. These results suggest that pretreatment PMI is useful for predicting outcomes for unresectable patients with APC undergoing systemic chemotherapy. Since the majority of previous reports have focused on the effect of skeletal muscle mass on survival for patients undergoing surgery, the results of the current study may be worth reporting (16,19-23).

For the baseline PMI values, the median PMI in males was 4.3 cm^2/m^2 (range, 1.6-8.2 cm^2/m^2), whereas in females it was 2.3 cm^2/m^2 (range, 0.7-6.1 cm^2/m^2). However, Hamaguchi *et al* (34) demonstrated that the PMI figure below two standard deviations of the mean among 541 healthy living donors for liver transplantation were 6.36 cm^2/m^2 for males and 3.92 cm^2/m^2 for females. When these cut-off values are applied to the current cohort, 55 patients (90.2%) were determined to have muscle mass loss. The significant discrepancy between the present data and the results of Hamaguchi *et al* (34) for baseline PMI may be attributed to the presence of advanced malignancies. Advanced malignancies themselves can cause severe muscle mass loss (17,18). Regarding comparison of baseline characteristics between the PMI-H and PMI-L groups, ECOG-PS and BMI were identified to be significant factors. DSMM is associated with disability, functional decline, poorer nutritional status and frailty, which may lead to poorer PS and lower BMI (13,14). However, aging was not identified to be a significant factor in the present study. Advanced malignancies, rather than just aging, may also affect skeletal muscle loss (17,18). The proportion of SAEs of grade ≥3 in the PMI-H group was higher, as compared with in the PMI-L group, although the difference in the two groups did not reach significance in the present study. The majority of previous studies demonstrated that DSMM can increase the risk of development of surgery-associated complications for patients with PC (16,19-23). Thus, caution for the development of SAEs during chemotherapy should be exercised, particularly in patients with PC with lower skeletal muscle mass.

CA19-9 was identified as an independent predictor for survival in the multivariate analysis. CA19-9 is the pancreatic cancer biomarker currently recommended for clinical use, and numerous reports have revealed that elevated CA 19-9 levels are associated with a worse survival rate, which are concordant with the results of the current study (35,40). In addition, CA19-9 levels in stage IVB patients were significantly higher compared with those in stage IVA patients (P=0.0060), as determined in the present study, which indicates that this biomarker effectively reflects tumor status. However, CRP is an inflammation marker and elevated CRP levels have been demonstrated to be adverse predictive factors in patients with solid malignancies (41). Although CRP was not identified to be significant in the present multivariate analysis, this marker may be important for predicting outcomes.

Clinical evidence that physical activity is beneficial for patients with solid malignancies in reducing chemotherapy-associated symptoms and improving quality of life, as well as drug tolerance and drug adherence for chemotherapy, has previously been reported (42). However, the effects of physical activity in patients with APC undergoing systemic chemotherapy remain unclear. Currently, a randomized controlled trial for investigating the impact of physical activity on outcomes in patients with APC is underway (43). If positive results are obtained in the study, treatment strategies for patients with APC receiving systemic chemotherapy may be altered in the future.

A number of limitations must be acknowledged with regard to the present study. Firstly, it was a retrospective observational study and biases inherent to retrospective analyses could not be completely removed. Secondly, the initial chemotherapeutic agents differed between the patients and these therapies could have potentially caused bias for clinical outcomes. Thirdly, the sample size was relatively small for analysis, potentially creating bias. Fourth, muscle quality as reflected by muscle strength was not evaluated in the current analysis. Finally, the present study population only included Japanese patients with PC with relatively low body weights compared with patients with PC in Western countries (18). Therefore, these results may not be directly applied to different ethnic populations. However, the results of the present study demonstrated that DSMM is associated with the clinical outcomes of patients with APC undergoing systemic chemotherapy.

In conclusion, DSMM as determined by PMI may be a significant predictor of prognosis in patients with APC receiving systemic chemotherapy. In such patients, appropriate interventions may be required for ameliorating the clinical outcome.

Acknowledgements

The authors would like to thank all medical staff at the Department of Internal Medicine, Hyogo College of Medicine (Nishinomiyashi, Japan) for their assistance.

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