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Sarcopenia is a reliable prognostic factor in patients with advanced pancreatic cancer receiving FOLFIRINOX chemotherapy

Yusuke Kurita [a, b], Noritoshi Kobayashi [b, *], Motohiko Tokuhisa [b], Ayumu Goto [b], Kensuke Kubota [a], Itaru Endo [c], Atsushi Nakajima [a], Yasushi Ichikawa [b]

[a] Department of Oncology, Yokohama City University School of Medicine, Yokohama, Japan
[b] Department of Gastroenterology and Hepatology, Yokohama City University School of Medicine, Yokohama, Japan
[c] Department Gastroenterological Surgery, Yokohama City University School of Medicine, Yokohama, Japan

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ABSTRACT

Background/objectives: FOLFIRINOX is the reliable treatments for pancreatic cancer, but it has a relatively high toxicity and the selection of suitable patients for this regimen remains challenge. On the other hand, sarcopenia is one of the important prognostic factors of pancreatic cancer. The aim of this study was to investigate the effect of sarcopenia on overall survival (OS) and time to treatment failure (TTF) in patients with pancreatic cancer who received FOLFIRINOX.

Methods: Clinical data of consecutive patients treated with FOLFIRINOX at our institution from 2011 to 2017 was retrospectively reviewed. Skeletal muscle index (SMI) and adipose tissue index (ATI) at the third lumbar spine level was calculated from computed tomography (CT) images. The association between clinical factors (SMI and ATI), and OS and TTF were determined using univariate and multivariate analyses.

Results: We assessed 82 patients. The median OS of sarcopenia and the non-sarcopenia patients were 11.3 and 17.0 months, respectively (hazard ratio [HR], 2.49; 95% confidence interval [CI], 1.43–4.32; $p = 0.001$). Median TTF was 3.0 and 6.1 months in the sarcopenia and the non-sarcopenia patients, respectively (HR, 1.67; 95% CI, 1.03–2.71; $p = 0.032$). Multivariate analyses revealed that sarcopenia (HR, 1.37; 95% CI, 1.01–1.87; $p = 0.045$) was an independent prognostic factor of OS. High ATI ($p = 0.022$) and sarcopenic obesity ($p = 0.008$) were significantly associated with hematologic toxicity.

Conclusions: Sarcopenia is an independent indicator of poor prognosis in patients with pancreatic cancer who received FOLFIRINOX, while ATI and sarcopenic obesity predicted severe hematologic toxicity.

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death worldwide. At the time of diagnosis, 80–85% of patients present with advanced unresectable disease [1]. A large proportion of pancreatic cancer patients have very poor prognosis with limited therapeutic options. Overall, the 5-year survival rate is only about 4% [2]. Hence chemotherapy is the mainstay of treatment for individuals with locally advanced pancreatic cancer (LAPC) or metastatic pancreatic cancer (MPC) with adequate performance status (but not helpful for those with poor performance status). The combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) have proven to be effective for advanced pancreatic cancer. FOLFIRINOX prolonged the median overall survival (OS) beyond the 6.8 months reported for gemcitabine, to 11.1 months [3]. The use of FOLFIRINOX has often been associated with intolerance because it frequently causes severe adverse events (AEs). Studies have showed that overall health is predictive of chemotherapy intolerance [3,4]. Once intolerance due to AEs occurs, chemotherapy must be discontinued and the prognosis is considered worse. Before starting on FOLFIRINOX,

Abbreviations: OS, overall survival; TTF, time to treatment failure; HR, hazard ratio; CI, confidence interval; SD, standard deviation; IQR, interquartile range; EOCG PS, eastern cooperative oncology group performance status; WBC, white blood cell; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CRP, c-reactive protein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; BMI, body mass index; SMI, skeletal muscle index; VATI, visceral adipose tissue index; SATI, subcutaneous adipose tissue index; ATI, adipose tissue index.

* Corresponding author. Department of Oncology Division, Yokohama City University School of Medicine, 3-9, Fuku-ura, Kanazawa-ku, Yokohama, 236-0004, Japan.
E-mail address: norikoba@yokohama-cu.ac.jp (N. Kobayashi).

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it is necessary to carefully check the condition of the patient. Poor nutritional status and weight loss during chemotherapy in cancer patients can be an adverse prognostic factor [4].

The state of decreased skeletal muscle is called sarcopenia. Sarcopenia is an independent poor prognostic factor of pancreatic cancer and other malignant tumors [5–8]. There are reports indicating that AEs tends to increase if skeletal muscle is small [9,10]. According to a previously reported study on the use of gemcitabine in patients with pancreatic cancer, sarcopenia was one of the important prognostic factors [11]. However, the effect of FOLFIRINOX on sarcopenia remains unclear. Therefore, the main aim of this study was to evaluate the effect of sarcopenia on OS and the time to treatment failure (TTF) in patients with advanced pancreatic cancer receiving FOLFIRINOX chemotherapy.

Methods

Patients and procedure

Using a computerized database, we analyzed data on patients diagnosed with pancreatic cancer at the Department of Oncology, Yokohama City University, from January 2011 to February 2017. Patients had histologically or cytological proven advanced pancreatic cancer.

Treatment

The treatment schedule of FOLFIRINOX comprised oxaliplatin, irinotecan, and leucovorin on day 1, followed by 5-FU as a bolus on day 1, and 2400 mg/m^2 5-FU as a 46-h continuous infusion biweekly. The doses of oxaliplatin, irinotecan, leucovorin, bolus 5-FU, and continuous 5-FU (85 mg/m^2, 180 mg/m^2, 400 mg/m^2, 400 mg/m^2, and 2400 mg/m^2, respectively) were administered. Modification of dose were made at the treating physician's decision based on toxicity and on patient preference. We used the Common Terminology Criteria for Adverse Events version 4.0. The dose reduction criteria due to toxicity were defined according to the number of AEs following the treatment. At the first, second, and third occurrence of an AE, bolus 5-FU was removed, and the dose of continuous 5-FU, oxaliplatin or irinotecan was reduced, respectively. Dose reduction was required for one or more of the following events: grade 4 neutropenia, febrile neutropenia, grade 4 thrombocytopenia, any other grade 3 or 4 toxicity, and delay of recovery from treatment-related toxicity for more than 2 weeks. If there was intestinal pneumonitis of any grade or grade 3 peripheral sensory neuropathy, chemotherapy was stopped. Treatment was discontinued when there was progression of disease, unacceptable toxicity, patient preference and alternative treatment such as surgical resection.

Data collection

Clinical data included age, sex, height, weight, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG PS), laboratory data (complete blood count with differential count and serum chemistry, albumin [Alb], alkaline phosphatase [ALP], lactate dehydrogenase [LDH], C-reactive protein [CRP], white blood cell [WBC]), and serum tumor markers (carcinoembryonic antigen [CEA], and carbohydrate antigen 19-9 [CA19-9]). The applied cut-off laboratory data for the assessed laboratory values were based on previously published reports [12–15]. In addition, we also considered the use of biliary tract stent, tumor site (head, body, and tail), metastatic site, previous treatment history, chemotherapy regimen, survival status, as well as the dates of chemotherapy administration and the date at last follow-up. The clinical data and laboratory data were measured within 4 weeks of chemotherapy initiation. Onodera 's prognostic nutritional index (PNI) was used as an indicator of nutritional status [16]. The PNI for each patient was calculated as 10 × serum albumin (g/dL) + 0.005 × lymphocyte count/μL. To assess for sarcopenia, we used adequate quality of abdominal computed tomography (CT) scan within 4 weeks of chemotherapy initiation. The diameter of primary pancreatic tumor and liver metastasis were measured using CT. The tumor volume of liver metastasis was classified as <10%, 10–30%, 30–50%, >50%.

Skeletal muscle and adipose tissue assessment

We analyzed CT images at the third lumbar vertebra (L3) using SYNAPSE Vincent (FUJI film, Tokyo, Japan). Using CT images, we determined the skeletal muscle and abdominal adipose tissue areas. Tissue Hounsfield unit (HU) thresholds were employed as follows: -29 to 150 HU for skeletal muscle and −150 to −30 for adipose tissue [17]. We calculated the skeletal muscle index (SMI) by normalizing the skeletal muscle area to height (m^2) and reported it as cm^2/m^2.

We also calculated the third lumbar vertebra (L3) total adipose tissue index (ATI) by normalizing the adipose tissue area to height (m^2) and reported it as cm^2/m^2. We defined L3 subcutaneous fat as L3 subcutaneous adipose tissue index (SATI) and L3 visceral fat as L3 visceral adipose tissue index (VATI) [18].

Endpoints

The primary endpoint of this study was OS defined as the time from the date of the 1st line chemotherapy initiation until death. Therefore, in the analysis of OS, we used the following clinical conditions: laboratory data and CT images within 4 weeks of initiation of 1st line chemotherapy. We defined the cut-off points for L3 SMI, which would best predict the mortality in this study using CT images within 4 weeks of initiation of 1st line chemotherapy in all case. This optimum stratification method has been previously used to determine the threshold value which separated two categories, such as sarcopenia and non-sarcopenia [19,20]. We used this method to find the most significant p value by using the log-rank test to define the sex-specific cut-off points associated with OS in our patients. L3 ATI, SATI, and VATI were also classified into two groups and examined using the optimum stratification method same as SMI. We also defined the group of sarcopenia and high ATI as sarcopenic obesity.

The secondary endpoint was TTF defined as the time from FOLFIRINOX treatment to treatment discontinuation for any reason (including disease progression, treatment toxicity, patient preference, change to other treatment, or death). In the analysis of TTF, we used the following clinical conditions: laboratory data and CT images within 4 weeks of FOLFIRINOX initiation. To perform the analysis on FOLFIRINOX AEs, data obtained within 4 weeks of FOLFIRINOX initiation was used. We defined intolerance as when chemotherapy continuation became impossible due to unacceptable AEs, patient preference, or physician's reluctance.

We also performed subgroup (LAPC group and MPC group) analysis. We included factors in the subgroup analysis which have shown significant differences in the main analysis.

Statistical analyses

OS and TTF were estimated using the Kaplan-Meier method, and differences between curves were evaluated using the log-rank test. For analysis of the association between sarcopenia and each factor, Mann-Whitney *U* test was used for continuous variables, and

Pearson's χ^2 test or Fisher's exact test for categorical data. Univariate analyses for OS and TTF were performed using log-rank test. Multivariate analyses were performed for factors that were significant at univariate analysis by Cox proportional hazard model. P value < 0.05 was considered significant. The statistical analyses were performed using SPSS (IBM, Armonk, NY, USA). The study was approved by the Institutional Review Board of Yokohama City University (B170300016).

Results

We recruited 87 patients from our institutional database. Five patients were excluded because of inadequate data. Accordingly, we assessed 82 patients retrospectively. Characteristics of the patients were summarized (Table 1). Median patient age was 64.0 (range, 40–80) years, with predominantly male patients 60 (73.1%). Initially, 53 (64.6%) patient had metastatic disease: (liver, 30 [36.6%], lung, 6 [7.3%], and peritoneum, 14 [17.1%]) while 10 patients (12.2%) had recurrent disease after curative resection. In total, 49 (59.7%) patients received FOLFIRINOX as 1st line and 33 (40.2%) patients either as second line chemotherapy or later lines.

The average SMI in all cases was 42.9 cm^2/m^2. The sex-specific average was 44.8 for males and 37.7 cm^2/m^2 for females. In this analysis, we defined sex-specific SMI-related mortality cut-off as 45.3 cm^2/m^2 and 37.1 cm^2/m^2 for men and women, respectively. We classified sarcopenia patients below these cut-offs for men and

Table 1
Patient characteristics and comparisons between patients with sarcopenia and non-sarcopenia.

Characteristic	No of patient (N = 82)	Sarcopenia n = 42	Non-sarcopenia n = 40	p
Age (years), median (range)	64.0 (40–80)	64.5 (40–78)	63.0 (43–80)	0.311
Gender male (%)	60 (73.1)	31	29	0.894
Site of tumor (%)				
Head	36 (43.9)	16	20	0.278
Body or tail	46 (56.1)	26	20	
EOCG PS (%)				
0	67 (81.7)	35	32	0.696
1	15 (18.3)	7	8	
Biliary drainage (%)	21 (25.6)	11	10	0.902
Primary tumor size (>30 mm)	49 (59.8)	27	22	0.391
Distant metastasis (%)	53 (64.6)	30	23	0.187
Liver metastasis	30 (36.6)	19	11	0.096
Tumor volume of liver metastasis (%)				
<10%	21 (25.6)	12	9	0.254
10–30%	8 (9.8)	6	2	
30–50%	1 (1.2)	1	0	
Lung metastasis	6 (7.3)	3	3	0.951
Peritoneum	14 (17.1)	7	7	0.920
Recurrent disease	10 (12.2)	3	7	0.189
Lines of FOLFIRINOX (%)				
First line	49 (59.7)	25	24	0.965
After second line	33 (40.2)	17	16	
Dose modifications of FOLFIRINOX				
At first	10 (12.2)	4	6	0.514
After the first cycle	72 (87.8)	38	34	
Previous chemotherapy before FOLFIRINOX (%)				
Gemcitabine monotherapy	13 (15.9)	6	7	0.690
Gemcitabine/S1	21 (25.6)	9	12	0.374
Gemcitabine/nab paclitaxel	2 (2.4)	1	1	1.000
S1 monotherapy	15 (18.3)	5	10	0.125
Post chemotherapy after FOLFIRINOX (%)				
Gemcitabine monotherapy	21 (25.6)	13	8	0.256
Gemcitabine/S1	3 (3.7)	2	1	1.000
Gemcitabine/nab paclitaxel	14 (17.1)	4	10	0.063
S1 monotherapy	8 (9.8)	2	6	0.150
Previous therapy before FOLFIRINOX (%)				
Pancreatectomy	10 (12.2)	3	7	0.189
Radiation (%)	12 (14.6)	5	7	0.474
Post therapy after introduction FOLFIRINOX (%)				
Pancreatectomy	5 (6.1)	1	4	0.138
WBC (/μl), median (IQR)	6450 (5300–7900)	6750 (5675–7950)	5850 (4750–7800)	0.132
Albumin (g/dl), median (IQR)	4.20 (3.80–4.40)	4.20 (3.90–4.43)	4.20 (3.63–4.40)	0.397
LDH (IU/L), median (IQR)	169.5 (147.8–198.0)	169.0 (146.0–202.5)	171.0 (148.0–194.0)	0.809
ALP (IU/L), median (IQR)	262.5 (202.5–359.3)	280.0 (229.3–357.3)	251.5 (189.0–364.5)	0.185
CRP (mg/dl), median (IQR)	0.13 (0.06–0.55)	0.20 (0.06–0.86)	0.10 (0.05–0.52)	0.213
CEA, (ng/ml), median (IQR)	4.50 (2.3–7.9)	4.85 (2.38–14.9)	3.90 (2.15–7.23)	0.268
CA19-9, (U/ml), median (IQR)	207.5 (26.5–1666.0)	475 (73.7–3524)	111.0 (15.3–670.0)	0.023
PNI, median (IQR)	48.7 (44.8–52.0)	49.2 (46.1–52.1)	48.5 (42.7–52.1)	0.303
BMI (kg/m^2), median (IQR)	21.7 (19.9–24.1)	21.4 (18.9–23.4)	21.7 (20.2–24.9)	0.021
SMI (cm^2/m^2), median (IQR)	43.1 (37.8–47.9)	39.0 (34.5–42.7)	48.0 (44.0–53.4)	<0.001
SATI (cm^2/m^2), median (IQR)	31.5 (19.6–46.3)	28.0 (15.0–38.4)	34.3 (20.7–53.4)	0.133
VATI (cm^2/m^2), median (IQR)	33.1 (16.4–54.3)	31.5 (9.4–45.3)	33.3 (17.8–58.2)	0.185
ATI (cm^2/m^2), median (IQR)	66.8 (36.1–103.4)	61.9 (29.2–87.0)	74.8 (45.8–108.5)	0.106

SD standard deviation, *IQR* interquartile range, *EOCG PS* eastern cooperative oncology group performance status, *WBC* white blood cell, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *CRP* c-reactive protein, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *BMI* body mass index, *SMI* skeletal muscle index, *VATI* visceral adipose tissue index, *SATI* subcutaneous adipose tissue index, *ATI* adipose tissue index, *PNI* prognostic nutritional index.

women. Overall, of 82 patients with assessable CT images, 42 (51.2%) had sarcopenia and the rest did not. Using the same method, we defined the male and female cut-off values for fat SATI (23.8 cm^2/m^2 versus 42.2 as cm^2/m^2), VATI (33.2 cm^2/m^2 versus 33.0 cm^2/m^2), and ATI (57.6 cm^2/m^2 versus 74.8 cm^2/m^2), respectively. The features of patients with sarcopenia and non-sarcopenia are also shown in Table 1. There was a statistically significant difference between BMI and CA 19-9 in sarcopenia group and non-sarcopenia group. There was no significant difference with liver metastasis, but there was a tendency that it was higher in the sarcopenia group than in the non-sarcopenia group ($p = 0.096$). There was also no significant difference in tumor volume of liver metastasis ($p = 0.254$).

There were no chemotherapy-related deaths. Twelve cases of intolerance were confirmed. Overall, 50 (61.0%) patients experienced grade 3 or 4 AEs. Major grade 3 or 4 AEs were hematologic toxicities 46 (56.1%) such as neutropenia 44 (53.7%), febrile neutropenia 4 (4.9%), anemia 5 (6.1%), and thrombocytopenia 2 (2.4%). The non-hematologic grade 3 or 4 toxicities 15 (18.3%) were fatigue 1 (1.2%), diarrhea 2 (2.4%), hyperglycemia 3 (3.7%), hyponatremia 1 (1.2%), elevated liver enzymes 1 (1.2%), and loss of appetite 6 (7.3%). Other severe AEs were pancreatitis 1 (1.2%) and pulmonary artery thrombosis 1 (1.2%). The relationship between the rate of AEs and sarcopenia before administration of FOLFIRINOX were also examined (Table 2). Statistically significant differences were found in fat mass (SATI [$p = 0.037$], VATI [$p = 0.042$], ATI [$p = 0.022$] and sarcopenic obesity [$p = 0.008$]) with hematologic toxicity. However, regarding non-hematologic toxicity, only SATI showed a statistically significant difference ($p = 0.020$). There was no association with intolerance in muscle mass and fat mass (Table 2).

The median OS for the 82 patients was 12.5 (95% confidence interval [CI], 8.8–16.1) months. Patients with sarcopenia (11.3; 95% CI, 9.4–13.0 months) showed significantly shorter median OS compared with patients with non-sarcopenia (17.0; 95% CI, 11.9–22.1 months) (Fig. 1a). Patients with sarcopenia (3.0; 95% CI, 2.1–3.8 months) showed significantly shorter median TTF compared with patients with non-sarcopenia (6.1; 95% CI, 1.8–10.5 months) (Fig. 1b).

Results of univariate analysis for OS are shown in Table 3. ECOG PS, ALP, CRP, CEA, liver metastasis, and sarcopenia (hazard ratio [HR], 2.49; 95% CI, 1.43–4.32; $p = 0.001$) were statistically significant. Variables with $p < 0.05$ in univariate analysis were selected for entry into the multivariate analysis. Importantly, ECOG PS and sarcopenia (HR, 1.37; 95% CI, 1.01–1.87; $p = 0.045$) were shown to be significant independent predictors of OS.

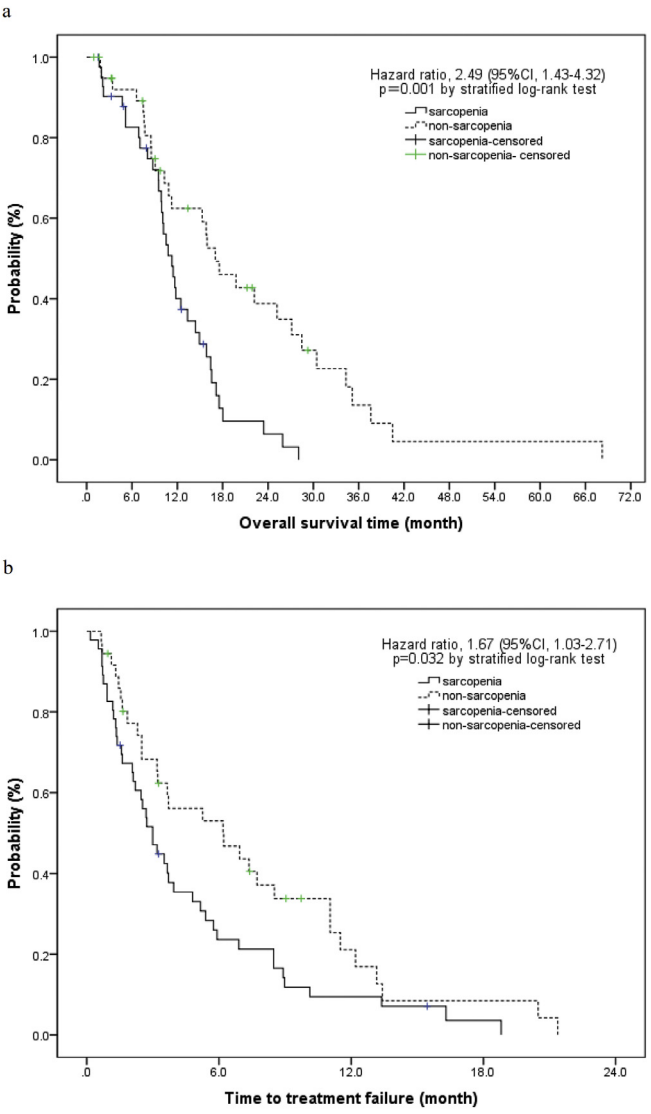

Fig. 1. Kaplan–Meier curves for (a) OS and (b) TTF with sarcopenia and non-sarcopenia.

Table 2
Risk of grade 3 or 4 toxicity FOLFIRINOX in relation to BMI, sarcopenia and ATI.

		Hematologic toxicity (grade 3 or 4)			Non-hematologic toxicity (grade 3 or 4)			Intolerance		
		Present	Absent	p	Present	Absent	p	Present	Absent	p
		n = 46	n = 36		n = 15	n = 67		n = 12	n = 70	
BMI	<22	27	21	0.974	6	42	0.107	7	41	0.988
	22≦	19	15		9	25		5	29	
Sarcopenia	present	30	16	0.060	10	36	0.362	7	39	0.866
	absent	16	20		5	31		5	31	
SATI	high	26	12	0.037	11	27	0.020	5	33	0.725
	low	20	24		4	40		7	37	
VATI	high	23	10	0.042	7	26	0.575	6	27	0.456
	low	23	26		8	41		6	43	
ATI	high	27	12	0.022	10	29	0.101	5	34	0.658
	low	19	24		5	38		7	36	
Sarcopenic obesity	present	17	4	0.008	6	15	0.194	3	18	1.000
	absent	29	32		9	52		9	52	

BMI body mass index, *VATI* visceral adipose tissue index, *SATI* subcutaneous adipose tissue index, *ATI* adipose tissue index.

Table 3
Univariate and multivariate analyses for OS and TTF.

		OS						TTF					
		Univariate			Multivariate			Univariate			Multivariate		
		HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age	<65	0.99	(0.60–1.61)	0.962				0.73	(0.45–0.73)	0.192			
	≥65	1						1					
Gender	Female	1.01	(0.59–1.72)	0.985				0.98	(0.75–1.27)	0.870			
	Male	1						1					
FOLFIRINOX first line		1.53	(0.91–2.56)	0.107				0.56	(0.35–0.89)	0.013	0.75	(0.45–1.25)	0.271
FOLFIRINOX after second line		1						1					
ECOG PS	1	1.81	(1.01–3.26)	0.044	1.98	(1.06–3.68)	0.031	1.64	(0.92–2.91)	0.093			
	0	1			1			1					
Site oftumor	body or tail	1.03	(0.80–1.32)	0.822				0.99	(0.79–1.26)	0.975			
	head	1						1					
Biliary drainage	absent	1.04	(0.78–1.38)	0.813				1.04	(0.80–1.36)	0.778			
	present	1						1					
Primary Tumor size	>30 mm	1.41	(0.84–2.35)	0.190				1.11	(0.69–1.80)	0.660			
	≤30 mm	1						1					
WBC	≥9000/μl	1.50	(0.94–2.39)	0.089				2.11	(1.03–4.30)	0.035	1.56	(0.62–3.94)	0.347
	<9000/μl	1						1			1		
Alb	<3.5 g/dl	0.83	(0.59–1.17)	0.288				1.58	(0.92–2.72)	0.094			
	≥3.5 g/dl	1						1					
LDH	≥225 U/l	1.33	(0.94–1.88)	0.109				0.98	(0.54–1.75)	0.942			
	<225 U/l	1						1					
ALP	≥334 U/l	1.33	(1.02–1.73)	0.035	1	(0.72–1.39)	0.999	1.8	(1.11–2.94)	0.016	1.24	(0.74–2.16)	0.450
	<334 U/l	1			1			1			1		
CRP	≥1.0 mg/dl	1.55	(1.12–2.14)	0.008	1.31	(0.91–1.90)	0.148	2.44	(1.40–4.26)	0.001	1.89	(0.93–3.87)	0.079
	<1.0 mg/dl	1			1			1			1		
CEA	≥5.0 ng/ml	1.37	(1.06–1.77)	0.018	1.24	(0.94–1.65)	0.131	2	(1.22–3.27)	0.005	1.41	(0.87–2.61)	0.141
	<5.0 ng/ml	1			1			1			1		
CA19-9	≥1000 U/ml	1.25	(0.94–1.64)	0.117				1.41	(0.86–2.30)	0.166			
	<1000 U/ml	1						1					
Liver metastasis	present	2.89	(1.68–5.01)	<0.001	1.84	(0.93–3.63)	0.081	2.41	(1.50–3.89)	0.001	1.77	(1.02–3.09)	0.044
	absent	1			1			1			1		
Lung metastasis	present	1.41	(0.51–3.91)	0.506				0.75	(0.32–1.74)	0.495			
	absent	1						1					
Peritoneum	present	1	(0.51–1.98)	0.990				0.95	(0.53–1.69)	0.860			
	absent	1						1					
Sarcopenia	present	2.49	(1.43–4.32)	0.001	1.37	(1.01–1.87)	0.045	1.67	(1.03–2.71)	0.032	1.34	(0.80–2.26)	0.270
	absent	1			1			1			1		
PNI	<40	0.85	(0.48–1.51)	0.583				1.04	(0.73–1.48)	0.817			
	≥40	1						1					
SATI	high	0.93	(0.57–1.53)	0.755				1.27	(0.80–2.03)	0.306			
	low	1						1					
VATI	high	0.67	(0.41–1.12)	0.124				1.21	(0.75–1.95)	0.413			
	low	1						1					
ATI	high	0.93	(0.56–1.53)	0.785				1.19	(0.75–1.89)	0.469			
	low	1						1					

OS overall survival, *TTF* time to treatment failure, *HR* hazard ratio, *CI* confidence interval, *EOCG PS* eastern cooperative oncology group performance status, *WBC* white blood cell, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *CRP* c-reactive protein, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *BMI* body mass index, *SATI* subcutaneous adipose tissue index, *VATI* visceral adipose tissue index, *ATI* adipose tissue index, *PNI* prognostic nutritional index.

We also performed univariate analysis and multivariate analysis for TTF. The results are shown in Table 3. FOLFIRINOX administration after the second treatment, elevated WBC, elevated ALP, elevated CRP, elevated CEA, liver metastasis, and sarcopenia (HR, 1.67; 95% CI, 1.03–2.71; $p = 0.032$) were statistically significant at univariate analysis. In the multivariate analysis, importantly, liver metastasis was a significant predictor of TTF. L3 SATI, L3 VATI, and L3 ATI were not associated with OS and TTF.

Furthermore, the subgroup analysis of sarcopenia was performed separately for LAPC and MPC. Factors in the subgroup analysis were lines of FOLFIRINOX, ECOG PS, WBC, ALP, CRP, CEA, liver metastasis, and sarcopenia, which differed significantly in the main analysis for OS and TTF. The results of the univariate analysis for OS and TTF in LAPC are shown in Table 4. In LAPC, the median OS for the 29 patients was 19.8 (95% CI, 11.5–28.1) months. In LAPC patients with sarcopenia, significantly shorter median OS (10.7; 95% CI, 8.8–12.7 months) compared with patients with non-sarcopenia (27.1; 95% CI, 19.9–34.3 months) was shown (Fig. 2a). Elevated WBC and sarcopenia (HR, 4.12; 95% CI, 1.47–11.55; $p = 0.004$) was statistically significant. In the multivariate analysis, only sarcopenia (HR, 3.85; 95% CI, 1.34–11.04; $p = 0.012$) was statistically significant. The median TTF (of 29 LAPC patients) was 4.8 (95% CI, 2.5–7.1) months. Patients with sarcopenia had shorter median TTF (2.5; 95% CI, 1.6–3.4 months) compared with patients with non-sarcopenia (11.0; 95% CI, 7.5–14.6 months) (Fig. 2b). In LAPC patients, at univariate analyses, findings showed significant association with TTF in lines of FOLFIRINOX, ECOG PS, elevated CEA and sarcopenia (HR, 4.11; 95% CI, 1.63–10.38; $p = 0.001$). In the multivariate analysis, sarcopenia (HR, 4.88; 95% CI, 1.69–14.02; $p = 0.003$) was shown to be an independent predictor of TTF in LAPC.

In 53 MPC patients, the median OS was 11.2 (95% CI, 9.7–12.8) months. There was no significant difference in OS between the sarcopenia (11.4; 95% CI, 9.5–13.4 months) and non-sarcopenia (10.8; 95% CI, 7.2–14.5 months) groups (Fig. 2c). Results of univariate analyses for OS and TTF in MPC are shown in Table 5. Elevated

Table 4
Univariate and multivariate analyses for OS and TTF of LAPC.

LAPC		OS						TTF					
		Univariate			Multivariate			Univariate			Multivariate		
		HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	P
FOLFIRINOX first line		2.29	(0.81–6.51)	0.112				2.58	(1.07–6.20)	0.027	1.29	(0.36–4.63)	0.698
FOLFIRINOX after second line		1						1					
ECOG PS	1	0.48	(0.06–3.73)	0.470				13.49	(1.22–148.8)	0.034	5.83	(0.51–65.68)	0.154
	0	1						1			1		
WBC	≥9000/μl	12.42	(1.12–137.3)	0.008	6.49	(0.57–73.73)	0.131	2.00	(0.26–15.53)	0.499			
	<9000/μl	1			1			1					
ALP	≥334 U/l	1.06	(0.61–1.86)	0.827				1.26	(0.51–3.14)	0.609			
	<334 U/l	1						1					
CRP	≥1.0 mg/dl	1.37	(0.48–3.90)	0.547				2.28	(0.61–8.46)	0.207			
	<1.0 mg/dl	1						1					
CEA	≥5.0 ng/ml	1.45	(0.90–2.35)	0.119				3.29	(1.25–8.63)	0.010	3.06	(0.71–13.15)	0.132
	<5.0 ng/ml	1						1			1		
Sarcopenia	present	4.12	(1.47–11.55)	0.004	3.85	(1.34–11.04)	0.012	4.11	(1.63–10.38)	0.001	4.88	(1.69–14.02)	0.003
	absent	1			1			1			1		

LAPC locally advanced pancreatic cancer, *OS* overall survival, *TTF* time to treatment failure, *HR* hazard ratio, *CI* confidence interval, *EOCG PS* eastern cooperative oncology group performance status, *WBC* white blood cell, *ALP* alkaline phosphatase, *CRP* c-reactive protein, *CEA* carcinoembryonic antigen.

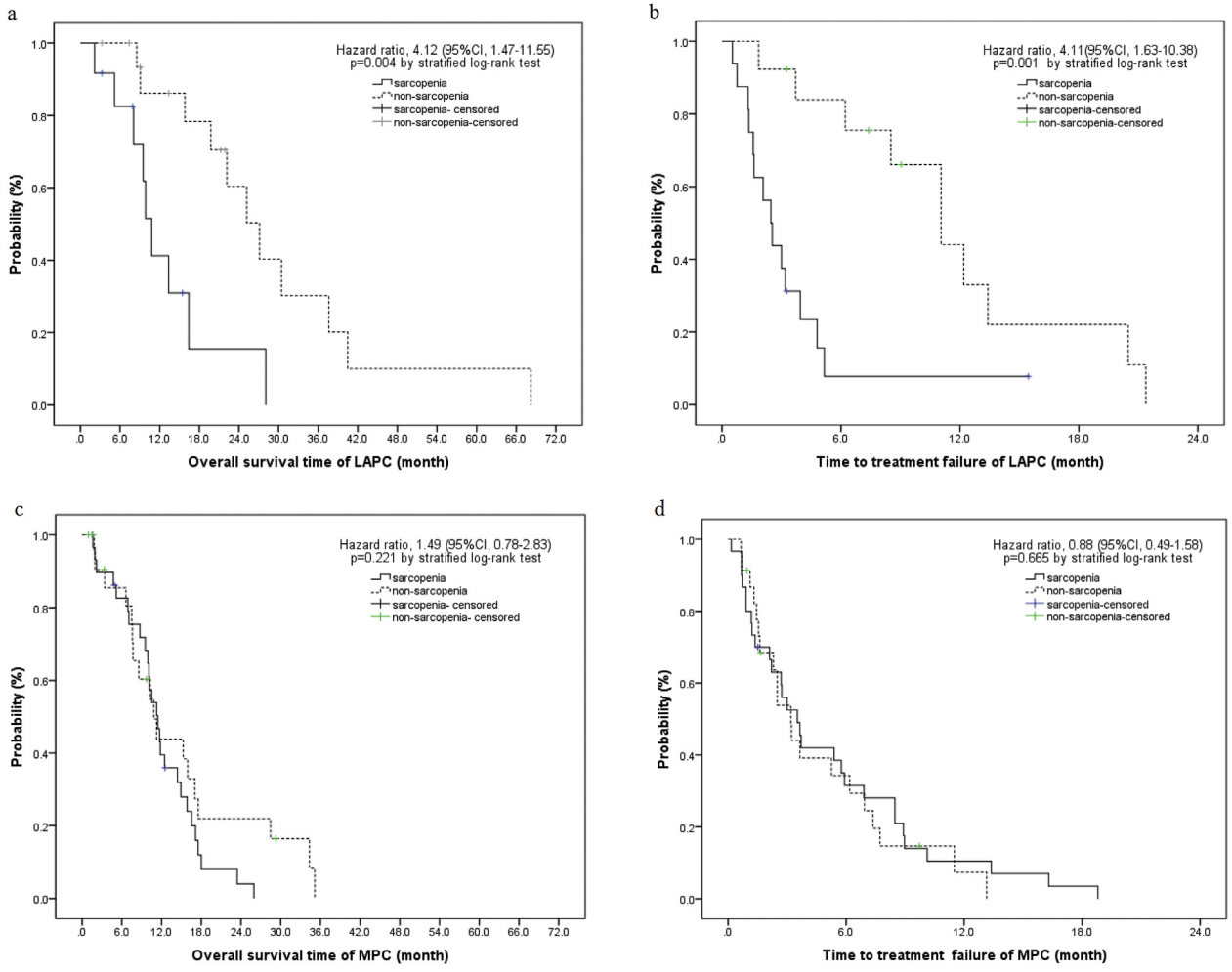

Fig. 2. Kaplan–Meier curves for (a) OS and (b) TTF in subgroup of LAPC with sarcopenia and non-sarcopenia.
Kaplan–Meier curves for (c) OS and (d) TTF in subgroup of MPC with sarcopenia and non-sarcopenia.

ALP and elevated CRP were statistically significant. Sarcopenia (HR, 1.49; 95% CI, 0.78–2.83; p = 0.221) was not statistically significant. In the multivariate analysis, Elevated ALP and elevated CRP were shown to be significant independent predictors of OS in MPC. The median TTF for the 53 patients was 3.2 (95% CI, 2.2–4.3) months in MPC. TTF of patients with sarcopenia (3.5; 95% CI, 2.2–4.8) months

Table 5
Univariate and multivariate analyses for OS and TTF of MPC.

MPC		OS						TTF					
		Univariate			Multivariate			Univariate			Multivariate		
		HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	P
FOLFIRINOX first line		1.47	(0.81–2.63)	0.192				1.21	(0.67–2.21)	0.520			
FOLFIRINOX after second line		1						1					
ECOG PS	1	1.28	(0.68–2.40)	0.436				2.10	(1.12–4.12)	0.019	2.56	(1.30–5.05)	0.007
	0	1						1			1		
WBC	≥9000/μl	1.86	(0.86–4.03)	0.110				1.49	(0.62–3.58)	0.515			
	<9000/μl	1						1					
ALP	≥334 U/l	2.09	(1.16–3.77)	0.012	1.95	(1.07–3.55)	0.029	2.05	(1.07–3.93)	0.027	2.05	(0.98–4.06)	0.054
	<334 U/l	1			1			1			1		
CRP	≥1.0 mg/dl	2.25	(1.20–4.26)	0.009	2.10	(1.10–4.00)	0.025	1.98	(0.99–3.94)	0.048	1.73	(0.82–3.62)	0.148
	<1.0 mg/dl	1			1			1			1		
CEA	≥5.0 ng/ml	1.53	(0.86–2.75)	0.145				1.54	(0.81–2.93)	0.180			
	<5.0 ng/ml	1						1					
Sarcopenia	present	1.49	(0.78–2.83)	0.221				0.88	(0.49–1.58)	0.665			
	absent	1						1					

MPC metastatic pancreatic cancer, *OS* overall survival, *TTF* time to treatment failure, *HR* hazard ratio, *CI* confidence interval, *EOCG PS* eastern cooperative oncology group performance status, *WBC* white blood cell, *ALP* alkaline phosphatase, *CRP* c-reactive protein, *CEA* carcinoembryonic antigen.

was not different from TTF of patients with non-sarcopenia (3.2; 95% CI, 2.2–4.2) months (Fig. 2d). In MPC, the univariate analysis results for TTF showed that poor ECOG PS, elevated ALP, and elevated CRP were statistically significant. Sarcopenia (HR, 0.88; 95% CI, 0.49–1.58; p = 0.665) was not statistically significant. In the multivariate analysis, poor ECOG PS was shown to be a significant independent predictor of TTF in MPC.

Discussion

FOLFIRINOX is a promising standard treatment for advanced pancreatic cancer. We mainly determined the correlation between sarcopenia with OS and TTF. In this study, TTF was defined as the period from the start of FOLFIRINOX treatment to treatment discontinuation for any reason (tumor progression, treatment toxicity, patient preference, or death). Severe nutritional problems including appetite loss, nausea, and body weight loss occurred in some patients on this treatment because of its strong toxicity [21], FOLFIRINOX frequently becomes intolerable due to AEs. We investigated for intolerable cases. In our study, intolerable cases were total twelve cases. Every intolerable cases decided as discontinuation by physician's judgment according to the Common Terminology Criteria for Adverse Events version 4.0. These cases were not so small, but sarcopenia was not correlated with FOLFIRINOX tolerability. On the other hand, tolerability of GEM-based chemotherapy was high in our institution (data was not shown). We deem FOLFIRINOX is more severe toxic and inflexible regimen than GEM-based chemotherapy. The factors of toxicity and inflexibility are not a direct assessment of the therapeutic effect of FOLFIRINOX, but we deem efficacy and tolerability of FOLFIRINOX is very important in this study. Therefore, we considered that the determining TTF was more important than progression-free survival in this study.

In patients with sarcopenia, reported AEs tend to occur [9,10,22]. In our study, although grade 3 or 4 hematologic toxicity AEs tended to occur to some extent in sarcopenia patients, there was no significant difference in the incidence of AEs with or without sarcopenia (p = 0.060). However, grade 3 or 4 hematologic toxicity AEs were observed more frequently in patients with high ATI and sarcopenic obesity. Current chemotherapy dosage is specified by the body surface area based on the height and weight. When the amount of fat is high, body weight tends to become heavy with fat. Therefore, the actual chemotherapy dose increases rather than the appropriate dosage for patients with high ATI; it is therefore suggested that the possibility of AEs is likely in high ATI. As previously reported in a study, AEs increase with obesity and sarcopenia [10]. In patients with high ATI or sarcopenic obesity, it may be preferable to reduce the dose of FOLFIRINOX appropriately so that the dose of chemotherapy does not become excessive. But, there is no standard modification method for the patients with sarcopenia and sarcopenic obesity. Now, we are planning the clinical trial for the patients with sarcopenia and sarcopenic obesity.

This is the first report showing that sarcopenia is an independent poor prognostic factor in pancreatic cancer patients receiving FOLFIRINOX. In this study, we found sarcopenia is poor prognostic factor in patients with pancreatic cancer who received FOLFIRINOX. Sarcopenia may be associated with the progressive loss of muscle [23]; put in another way, sarcopenia could be referred to as 'muscle loss'. 'Muscle loss' is a most important prognostic factor in patients with pancreatic cancer who received FOLFIRINOX.

TTF was also associated with SMI in this study. Comparing LAPC and MPC groups, the MPC disease condition is generally more advanced than the LAPC disease condition. The prognosis is better in LAPC than MPC with the introduction of FOLFIRINOX [24]. OS and TTF in LAPC showed significant difference depending on whether it was sarcopenia or not in our study. On the other hand, in MPC, sarcopenia was not a significant factor of OS and TTF. LAPC with non-sarcopenia should have a better general condition than MPC, hence, it is considered that OS and TTF was achieved longer period. LAPC with sarcopenia may lead to a worse condition similar with MPC. Sarcopenia may be as important prognostic factor as tumor spread to other organs. Hence, we should be more careful in selecting FOLFIRINOX for LAPC with sarcopenia. ALP is considered a prognostic factor in pancreatic cancer and other cancers [25–27]. ALP and CRP have recently been reported to play important roles in tumor growth [28,29]. Therefore, especially in liver metastasis, elevated ALP and elevated CRP with tumor progression in MPC resulted. For this reason, ALP and CRP have a stronger influence on OS than sarcopenia in MPC. In MPC, only PS was a factor related to TTF. Poor ECOG PS is not because of sarcopenia, suggesting that muscle loss does not always mean poor performance status. We found several prognostic factors in patients with advanced pancreatic cancer who received FOLFIRINOX. The prognostic factors are readily available information while treating pancreatic cancer; moreover, we expect that the use of the findings of this study will be relevant when deciding based on clinical stratification.

In this study, more than half of patients were defined as sarcopenia. Malnutrition, pain, infection and decrease in physical activity were important factors of sarcopenia. In pancreatic cancer, the nutritional impairment due to the insufficiency of pancreatic exocrine and endocrine function, other metabolic factor, pain and infection such as cholangitis and febrile neutropenia may have promoted the development of sarcopenia. Although this study does not conclude the prevention of sarcopenia, it is important to treat such nutritional problems, pain and infection prevent the promotion of sarcopenia.

Our study had several limitations. First, it was retrospective and had a small sample size. Second, the limitation occurred based on the evaluation of both the first-line and second-line chemotherapy treatments. Third, important limitations were the threshold values with sarcopenia. There are various methods for measuring muscle mass using CT, such as total muscle mass of L 3 [7], iliopsoas muscle area of L 3 [30], things using volume of the iliopsoas muscle [31], and unification method for measuring muscle has not been established. Previous Western studies defined the cut-off values of sarcopenia related to poor prognosis using SMI [10,32,33]. However, we did not adopt the Western studies values because Asian studies reported that the cut-off values of sarcopenia from previous Western studies were inappropriate for Asian patients [11,34]. In Western studies report, sarcopenia was defined as SMI cut-off of 52.4 cm^2/m^2 in men and 38.5 cm^2/m^2 in women [19]. The definitions of SMI from Western study may not be suitable to Japanese pancreatic cancer patients because they differ from western populations. Although Asian Working Group for Sarcopenia recommended cutoff values for various other methods of muscle mass measurements [35], the unified sarcopenia cutoff in Asian, including the SMI method using CT, remains unclear. The method and cutoff value may be different from cohort to cohort. Therefore, it is considered important to define the cutoff value for each disease or each cohort. Meta-analysis of cut off value of sarcopenia for other cancers has been reported [36,37], but there is no report of cutoff value of sarcopenia for meta-analysis in pancreatic cancer. The definition of sarcopenia in Japanese pancreatic cancer is not clear yet. Therefore, in the present study, sarcopenia was defined using a statistical analysis cut-off of <45.3 cm^2/m^2 for men and <37.1 cm^2/m^2 for women; this point is therefore a limitation of our study. Therefore, we believe that the definition of sarcopenia and the cut-off value of this study will be applicable only to advanced pancreatic cancer. In many cases, patients with pancreatic cancer may be sarcopenia compared with normal adults. Therefore, when considering the treatment of pancreatic cancer, it is better to use the sarcopenia value peculiar to pancreatic disease rather than the sarcopenia value of normality as in this study. It is desirable to study the optimal cut-off of SMI to be able to define sarcopenia cut-off values for Asians with pancreatic cancer. And there was another limitation, there was a tendency that liver metastasis was higher in the sarcopenia group than in the non-sarcopenia group ($p = 0.096$), although there was not significant difference in tumor volume of liver metastasis. There is not so enough evidence about the relationship tumor burden and sarcopenia.

In conclusion, sarcopenia indicates poor prognosis in patients receiving FOLFIRINOX for advanced pancreatic cancer. In particular the results of this study suggest that LAPC patients with sarcopenia may be as worse prognosis as patients MPC. While, LAPC patients with non-sarcopenia, without high ATI, FOLFIRINOX can be a good indication.

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