Pentraxin 3 is an adipose tissue-related serum marker for pancreatic cancer cachexia predicting subsequent muscle mass and visceral fat loss

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Abstract
Cancer cachexia, a paraneoplastic syndrome characterized by ongoing skeletal muscle mass loss, is accompanied by adipose tissue loss and strongly affects chemotherapy endurance. Our aim was to detect a serum marker reflecting pancreatic cancer cachexia and predicting subsequent loss of muscle mass and adipose tissue, focusing on adipose tissue-secreted proteins. Murine-derived pancreatic cancer cells were orthotopically injected into the mouse pancreatic tail. After 3 weeks, RNA sequencing of perigonadal fat and orthotopic tumors was carried out. We analyzed stocked sera and clinical data of metastatic pancreatic cancer patients who received chemotherapy. Perigonadal fat weight/body weight decreased in mice with orthotopic tumors compared to those without tumors. By RNA sequencing and real-time PCR validation, pentraxin 3 (PTX3) was identified as a secreted protein-encoded gene whose expression was significantly higher in the perigonadal fat of mice with orthotopic tumors than in that of mice without orthotopic tumors and was least expressed in orthotopic tumors. Serum PTX3 levels correlated with PTX3 mRNA levels in perigonadal fat and were higher in mice with orthotopic tumors than in those without tumors. In 84 patients diagnosed with metastatic pancreatic cancer, patients with high serum PTX3 levels showed a greater visceral fat loss/month and skeletal muscle mass index (SMI) decrease/month than those with low serum PTX3 levels. High serum PTX3 was an independent risk factor for visceral fat loss, decreased SMI, and poor prognosis. High serum PTX3 in pancreatic cancer patients predicts visceral fat and muscle mass loss and major clinical outcomes of cancer cachexia.
1 | INTRODUCTION

Pancreatic cancer is one of most deadly cancers, with a 5-year survival rate of 10%. Approximately 50% of pancreatic cancers have distant metastases at diagnosis, and the 5-year survival of patients with distant metastasis is as low as 3%. Combination chemotherapy, including gemcitabine/albumin-bound paclitaxel and FOLFIRINOX, has become the standard chemotherapy for patients with metastatic pancreatic cancer, prolonging the MST from approximately 6 months to 9–11 months. In multidrug chemotherapy, where patients experience more severe adverse events than those with a single drug regimen, the patient's chemotherapy endurance is important. Patients with cancer cachexia experience more frequent adverse events than those without cachexia. Which patients benefit from and can endure multidrug chemotherapy is closely related to cancer cachexia, and detecting the presence of cancer cachexia remains a major issue.

Cancer cachexia is clinically characterized by an ongoing loss of skeletal muscle mass. Approximately 70%–80% of pancreatic cancer patients have been reported to suffer from cachexia. Cachexia also decreases quality of life. As a result, 10%–20% of cancer deaths are due to cachexia-induced malnutrition rather than malignancy itself. Up to 40% of cancer patients present with weight loss, the major clinical sign of cachexia. Regarding the underlying molecular mechanism, cancer cachexia is an ongoing systemic inflammatory syndrome triggered by a variety of tumor-secreted inflammatory factors. For this reason, cancer-derived cytokines, including tumor necrosis factor, IL-1, and IL-6, have been major targets of study for detecting the presence of cancer cachexia. However, these cytokine levels do not necessarily correlate with skeletal muscle loss or bodyweight loss and are not good markers of cancer cachexia. Not only skeletal muscle but also various organs throughout the body are affected by cancers in patients suffering from cancer cachexia, and the response in these organs affected by cancers could reflect the extent of cancer cachexia. Cancer cachexia disrupts adipose tissue metabolism, and adipose tissue loss is one of the first symptoms of cancer cachexia. However, there are few reports focusing on adipose tissue-derived markers for cancer cachexia. In the present study, we focused on adipose tissue and aimed to find a clinical serum marker that can detect pancreatic cancer cachexia before skeletal muscle mass loss or bodyweight loss.

2 | MATERIALS AND METHODS

2.1 | Cell culture and in vitro experiments

The murine pancreatic cancer cell line mPKC1 was established from the genetically engineered pancreatic cancer mouse model ElaCre KrasLSL G12D trp53fl/fl EYFPTr/Tr as previously reported. mPKC1 was cultured in DMEM (D5796; Sigma–Aldrich). The 3T3-L1 cell line was purchased from JCRB (JCRB0914). The pancreatic cancer cell lines PANCl (CRL 1469), MiaPaCa-2 (CRL-1420), AsPC-1 (CRL-1682), HPAF-II (CRL-1997), and BxPC3 (CRL-1687) were obtained from ATCC. The liver tumor cell lines HepG2 (HB-8065) and Hep3B (HB-8064) were purchased from ATCC. The liver tumor cell line HuH-7 (JCRB0403) was obtained from JCRB.

Upon experimental use, all 3T3-L1 cells were differentiated into lipid-rich adipose tissue cells according to the protocol below. The 3T3-L1 cells were first seeded in low-glucose DMEM (#08456-36; Nacalai Tesque). Forty-eight hours after reaching confluency, the culture medium was changed to differentiation medium: low-glucose DMEM with 0.5 mM 3-isobutyl-1-methylxanthine (#I7018; Sigma–Aldrich), 1 μM dexamethasone (#D4902; Sigma–Aldrich), and 5 μM insulin (#I1882; Sigma–Aldrich). After 48 h of incubation in differentiation medium, the medium was changed to maintenance medium: low-glucose DMEM with 5 μM insulin. For coculture experiments, mPKC1 cells were seeded in cell culture inserts (#3401; Corning) and cocultured with differentiated 3T3-L1 cells. All media were supplemented with 10% FBS and 1% penicillin/streptomycin.

2.2 | Real-time PCR

RNA was extracted and reverse transcribed to cDNA using an RNeasy kit (#74106; Qiagen) and PrimeScript reverse transcriptase (#2680; TaKaRa). The TaqMan assay primers (Thermo Fischer Scientific) used are listed in Table S1. Thunderbird probe qPCR mix (QPS-101; Toyobo) was used for real-time PCR. Gene expression was measured with a QuantStudio 6 Flex real-time PCR system (Thermo Fischer Scientific) and was normalized to β-actin expression.

2.3 | Enzyme-linked immunosorbent assay

For murine ELISAs, a PTX3 ELISA kit (ab245713; Abcam) and Mouse SRPX ELISA kit (MBS9325724; My BioSource) were used. The PTX3 level in the cell culture supernatant was also measured with a murine PTX3 ELISA kit (ab245713; Abcam). A NEFA C Test Wako (#279-75401; Fujifilm Wako Pure Chemical Corporation) was used for NEFA measurement. Human serum was assayed with a Human Pentraxin 3/PTX3 ELISA Kit (ab214570; Abcam) and NEFA C Test (#279-75401; Fujifilm Wako Pure Chemical Corporation) according to the manufacturers’ protocols.

2.4 | Animal experiments

C57BL6/J mice were purchased from Charles River Japan at 5 weeks of age. All mice used in our study were male. Mice were raised on an HFD from 5 to 15 weeks of age. At that time, 5 × 10⁵ mPKC1 cells
eluted in 25 μl Matrigel (356230; Corning) were injected orthotopically into the pancreatic tail. After orthotopic injection, the mice were fed HFD. At 18 weeks of age, 3 weeks after orthotopic injection, the mice were killed for analysis. Some mice were continually raised after 18 weeks of age and killed to evaluate overall survival. All mice used in our study were anesthetized with midazolam (0.4 mg/ml), butorphanol (0.5 mg/ml), and medetomidine (75 μg/ml) at the time of orthotopic injection and death. All measures possible were taken to lessen suffering. All animal experiments were approved by the institutional committee (approval number: 30–015) and conducted according to the approved protocol.

2.5 | RNA sequencing

RNA was extracted from orthotopic tumors and perigonadal fat of mice with or without orthotopic injection as described above using an RNeasy kit (#74106; Qiagen). RNA sequencing was undertaken using these samples as previously described.21

2.6 | Clinical data

Metastatic pancreatic cancer patients who were treated at Osaka University Hospital from September 2014 to December 2020 were identified from conference records. Among the listed patients, those who provided informed consent and agreed to preserve serum before first-line chemotherapy were enrolled. Pretreatment laboratory data of the enrolled patients were collected from medical records. The NLR,22–25 PLR,26,27 mGPS,28–30 and PNI31,32 were calculated as reported inflammatory laboratory parameters affecting prognosis. For mGPS (score 0, CRP ≤1.0 mg/dl; score 1, albumin ≥3.5 g/dl and CRP >1.0 mg/dl; and score 2, albumin <3.5 g/dl and CRP >1.0 mg/dl), we divided the patients into those with a score of 0 and those with scores of 1–2. We considered the cut-off value of CRP to be 1.0 mg/dl and albumin to be 3.5 g/dl according to the mGPS. For other variables without a definite cut-off value, including the NLR, PLR, and PNI, the median of the 84 patients enrolled was used as the cut-off value. Computed tomography within 2 months of chemotherapy induction and CT 2 months after chemotherapy induction with an allowance of 1 month were used to calculate the change in SMI, visceral fat occupation area, and subcutaneous fat occupation area (Figure S1). In the calculation of skeletal muscle, visceral fat, and subcutaneous fat, we evaluated the CT slice at the height of the third lumbar vertebra using SliceOmatic software (Tomovision) and mechanically calculated the occupation area using the ABACS module.33 Skeletal muscle was standardized to the square of the height in meters to obtain the SMI. The occupation area before chemotherapy induction was described as pre-SMI, previsceral fat, and presubcutaneous fat in this study. Ten patients without a history of cancer who were hospitalized with colon polyps were randomly selected and used as controls. Stage 0–III patients who were treated at Osaka University Hospital from September 2014 to December 2020 were listed from conference records. Serum PTX3 levels of those who provided informed consent and agreed to preserve serum before treatment were analyzed. This study followed the Declaration of Helsinki and was approved by the Institutional Review Board of Osaka University (approval no. 17160).

2.7 | Statistical analysis

All in vitro experiments were independently carried out more than three times using biological replicates. In our in vivo and in vitro experiments, we evaluated normality by the Shapiro–Wilk test. Data with a normal distribution were analyzed with two-tailed Student’s t-tests. Those without a normal distribution were evaluated by the Mann–Whitney U-test and are described in the figure legends. For clinical data, continuous variables were analyzed with the Mann–Whitney U-test, and categorical variables were analyzed with the χ²-test. The association of variables was determined by logistic regression analysis. Prognostic factors were analyzed using a Cox proportional hazard model. Overall survival was estimated with the Kaplan–Meier method and evaluated with the log-rank test. Correlation was analyzed using the Pearson correlation coefficient. All statistical analyses were undertaken with JMP Pro 15 (SAS Institute, Inc.). We considered a p value below 0.05 to be significant.

3 | RESULTS

3.1 | Orthotopic pancreatic tumors induced perigonadal fat loss with lipid metabolic changes in immunocompetent mice

C57Bl6/J mice were fed HFD from 5 weeks of age. At 15 weeks of age, these mice were orthotopically injected with mPKC1, a murine pancreatic cancer cell line. All orthotopically injected mice formed orthotopic tumors, suffered bodyweight loss, and were killed due to the tumor burden at 22–57 days after orthotopic injection (Figure S2A,B). At 18 weeks of age, not only the bodyweight but also the perigonadal fat weight per bodyweight was significantly lower in the mice with orthotopic tumors than in those without tumors (Figure 1A,B), suggesting perigonadal fat loss by orthotopic tumors. In the perigonadal fat of mice at 18 weeks of age, the mRNA expression of characteristic markers of lipid metabolism, namely, Acsl1, CD36, Fasn, LPL, PPARg, and adiponectin, was decreased by orthotopic injection (Figure 1C). The median mRNA expression levels of other lipid metabolism characteristic markers, that is, Acaca and FABP4, were decreased (Figure 1C), although the difference was not significant. The serum level of NEFAs, mainly released from adipose tissues, also decreased in the mice with orthotopic tumors compared to those without tumors (Figure 1D).
3.2 | RNA sequencing of adipose tissues detected candidate serum biomarkers for perigonadal fat and bodyweight loss

To detect an adipose tissue-specific serum biomarker for perigonadal fat loss that is least affected by the orthotopic tumor itself, we undertook RNA sequencing of both perigonadal fat and the orthotopic tumor itself in mice at 18 weeks of age. Among 2041 genes whose FPKM in perigonadal fat extracted from the mice with orthotopic tumors was 1.5 times or more compared to those without tumors and whose FPKM was over 10 in the perigonadal fat of the mice with orthotopic tumors, 104 genes were described as secreted proteins in the Human Protein Atlas (www.proteinatlas.org) (Figure S3). After excluding genes with FPKM > 10 in the orthotopic tumor itself to minimize the effect of secretion from the orthotopic tumor, we identified three genes, namely, PTX3, Sfrp2, and Srpx, as candidates for adipose tissue-derived serum biomarkers for perigonadal fat loss. Increased mRNA expression of PTX3 and Srpx in the perigonadal fat of the mice with orthotopic tumors compared to those without tumors was confirmed by real-time PCR (Figure 1E). Serum ELISAs showed an increase in PTX3 but not Srpx concentrations in the mice with orthotopic tumors compared to those without tumors (Figure 1F). The mRNA expression of PTX3 in perigonadal fat correlated with the serum PTX3 level (Figure 1G). The serum PTX3 level negatively correlated with the perigonadal fat weight per bodyweight (Figure 1H), suggesting a correlation with perigonadal fat loss. This parameter was also negatively correlated with the bodyweight change from 15 weeks to 18 weeks of age, as well as the body weight at 18 weeks of age (Figure 1H). While the serum NEFA level was negatively correlated with the serum PTX3 level, no correlation between the orthotopic tumor weight and serum PTX3 level was detected (Figure 1H).

3.3 | Adipose tissue cells increased PTX3 secretion when cocultured with cancer cells

We cocultured mPKC1 pancreatic cancer cells with differentiated 3T3-L1 adipose tissue cells. Upon coculture with mPKC1, the mRNA expression of Acaca, Acsl1, CD36, FABP4, Fasn, LPL, PPARG, and adiponectin in 3T3-L1 adipose tissue cells decreased, consistent with our mouse experiments (Figure S4A). The mRNA level of PTX3 in 3T3-L1 cells increased when they were cocultured with mPKC1 (Figure S4B). The coculture supernatant of 3T3-L1 cells with mPKC1 cells had a higher concentration of PTX3 than that of monocultured 3T3-L1 cells (Figure S4C). Pentraxin 3 was not detected in the supernatant of monocultured mPKC1 cells (Figure S4C).

The mRNA expression levels of PTX3 in mPKC1 cells were below the detection limits (Figure S4B). When we looked at human pancreatic cancer cell lines, PANC-1 and MiaPaCa-2 showed higher PTX3 expression compared with BxPC3, AsPC-1, and HPAF-II. 3T3-L1 adipose tissue cells expressed higher PTX3 mRNA expression than all of these cell lines (Figure S5). 3T3-L1 adipose tissue cells also expressed higher PTX3 mRNA expression than human liver tumor cell lines Hep-G2, Huh7, and Hep-3B (Figure S5).

3.4 | Serum PTX3 levels correlated with visceral fat loss and SMI loss in pancreatic cancer patients

Among 170 consecutive patients diagnosed with unresectable pancreatic cancer and treated with chemotherapy at Osaka University Hospital from September 2014 to December 2020, 64 patients without serum before chemotherapy, 7 patients who continued chemotherapy in a different hospital, and 15 patients with locally advanced cancer were excluded (Figure S6). A total of 84 patients with distant metastasis treated with chemotherapy had serum PTX3 levels measured at baseline. Two patients without CT after chemotherapy induction were excluded from the analysis of changes in the CT occupation areas (Figure S6). The median level of serum PTX3 was 734 ng/ml. Serum PTX3 levels in the patients with metastatic pancreatic cancer were higher than those in the control colon polyp patients without any history or presence of cancer (Figure 2A). Elevations in serum PTX3 compared with control patients were only seen in stage IV metastatic patients and not in stage 0, I, II, or III patients (Figure S7). Further analysis was carried out with patients with distant metastasis. The serum NEFA levels were lower in metastatic pancreatic cancer patients than in colon polyp patients (Figure 2B).

We divided these patients into a high serum PTX3 group and a low serum PTX3 group using the median level of serum PTX3. The high serum PTX3 patients had higher NLR, PLR, mGPS, CRP, and CA19-9 and lower albumin levels at baseline than the patients with low serum PTX3 levels (Table 1). No change in clinical stage or background medical history, including diabetes, was observed between...
High serum PTX3 was a risk factor for visceral fat loss and SMI loss in pancreatic cancer patients

We then investigated whether PTX3 is a marker of visceral fat loss and SMI loss, the two clinical components of cancer cachexia. Among a total of 82 patients, 35 patients had visceral fat loss of over 5% per month. Univariate analysis showed that an mGPS score of 1–2, high CRP, and high PTX3 were factors related to visceral fat loss over 5% per month. High CRP and mGPS scores of 1–2 were found in the same cohort, so we used CRP for multivariate analysis. Upon multivariate analysis, high PTX3 (HR 5.19, \( p = 0.002 \); Table 2) was the only factor. Among a total of 82 patients, 43 patients suffered an SMI decrease. In univariate analysis, high PTX3 and high pre-SMI were the factors related to the SMI decrease. Upon multivariate analysis, high PTX3 was the only factor detected (HR 9.43, \( p < 0.001 \); Table 3).

PTX3 was identified as a prognostic marker for metastatic pancreatic cancer patients

We examined PTX3 and its effect on prognosis in patients with metastatic pancreatic cancer. Upon univariate analysis, an mGPS score of 1–2, low PNI, low albumin, high CRP, high CA19-9, and high PTX3 were prognostic factors. C-reactive protein and albumin both showed value in our analyses and are confounding factors of mGPS. To avoid bias, we independently analyzed CRP and albumin instead of mGPS for further analysis. Multivariate analysis showed that high PTX3 (HR 1.70, \( p = 0.047 \)) and high CRP (HR 2.02, \( p = 0.040 \)) were prognostic factors (Table 4). The MST of all 84 patients was 264.5 days. High PTX3 (Figure 2D) and high CRP (Figure 2D) shortened the overall survival. The median first-line chemotherapy treatment time of all 84 patients was 119 days. High PTX3 (Figure 2E) and high CRP (Figure 2E) shortened the first-line chemotherapy treatment time.

4 | DISCUSSION

In the present study, we clarified that serum PTX3 is a marker for muscle and adipose tissue loss in patients with pancreatic cancers. Given that loss of skeletal muscle mass is a characteristic feature of cancer cachexia and that adipose tissue loss is a first symptom of cancer cachexia,18,19 serum PTX3 can reflect the presence of cancer cachexia. Researchers have shown that changes in skeletal muscle area correlate negatively with disease-free survival and that adipose tissue loss worsens overall survival and progression-free survival.33 In unresectable pancreatic cancer patients treated with FOLFIRINOX or gemcitabine-based regimens, a decrease in the SMI from first-line chemotherapy induction to the first follow-up CT was reported to worsen prognosis.34 Not sarcopenia at diagnosis but a decrease in the SMI from prechemotherapy to the first follow-up CT was a prognostic factor in unresectable pancreatic cancer patients.35 Thus, muscle mass loss and adipose tissue loss, indicating cachexia severity, deeply affect disease-free survival or prognosis in pancreatic cancer patients. Consistent with these reports, serum PTX3 was an independent risk factor for poor prognosis in the present study. For pancreatic cancer treatment, monitoring the presence of cancer cachexia by measuring serum PTX levels would be clinically useful.

Pentraxin 3 is an important mediator of innate immunity. The tumor-induced inflammatory response causes anorexia, leading to bodyweight loss and deteriorated physical function.36 Unlike CRP, which is mainly produced in the liver upon IL-6 stimulation, PTX3 is secreted by multiple kinds of cells, including dendritic cells, monocytes, macrophages, fibroblasts, adipocytes, and smooth muscle cells.37 In our in vivo data, the mRNA expression of PTX3 in periglandular fat correlated with serum PTX3 levels, showing that adipose tissue-derived PTX3 could play an important role in the elevation of serum PTX3 levels in pancreatic cancer patients (Figure 1G). In acute inflammation, PTX3 was reported to act as a rapid turnover response protein and has been reported to be an effective marker for local inflammation, including acute myocardial infarction, to systemic inflammation, such as sepsis.38 Our human data showed a correlation between serum PTX3 levels with all inflammatory variables analyzed, including NLR, PLR, PNI, Alb, and CRP, showing a strong
| Variable                        | All patients (n = 84) | PTX3 low group (n = 42) | PTX3 high group (n = 42) | p Value |
|--------------------------------|-----------------------|-------------------------|--------------------------|---------|
| Sex                            |                       |                         |                          |         |
| Male/female                    | 45/39                 | 20/22                   | 25/17                    | 0.274   |
| Age, years                      |                       |                         |                          |         |
| Median (range)                  | 69.5 (43–81)          | 70.5 (43–80)            | 68 (43–81)               | 0.159   |
| Follow-up period, days          |                       |                         |                          |         |
| Median (range)                  | 264.5 (14–1782)       | 358.5 (72–1782)         | 212.5 (14–638)           | 0.003   |
| BMI, kg/m²                      |                       |                         |                          |         |
| Yes/no                          | 21.2 (13.3–29.2)      | 21.1 (15.7–26.1)        | 21.3 (13.3–29.2)         | 0.879   |
| ASA PS, class                   |                       |                         |                          |         |
| 1/2/3                           | 34/47/3               | 15/26/1                 | 19/21/2                  | 0.513   |
| Smoking                         |                       |                         |                          |         |
| Yes/no                          | 31/53                 | 17/25                   | 14/28                    | 0.498   |
| Alcohol                         |                       |                         |                          |         |
| Yes/no                          | 46/38                 | 21/21                   | 25/17                    | 0.381   |
| Diabetes mellitus               |                       |                         |                          |         |
| Yes/no                          | 25/59                 | 12/30                   | 13/29                    | 0.811   |
| Hypertension                    |                       |                         |                          |         |
| Yes/no                          | 31/53                 | 19/23                   | 12/30                    | 0.114   |
| Dyslipidemia                    |                       |                         |                          |         |
| Yes/no                          | 17/63                 | 6/36                    | 11/31                    | 0.175   |
| Hyperuricemia                   |                       |                         |                          |         |
| Yes/no                          | 9/75                  | 3/39                    | 6/36                     | 0.290   |
| Tumor size, mm                  |                       |                         |                          |         |
| Median (range)                  | 35 (10–90)            | 37 (15–90)              | 33 (10–74)               | 0.423   |
| Location of tumor               |                       |                         |                          |         |
| Head/body or tail               | 33/51                 | 15/27                   | 18/24                    | 0.503   |
| Obstructive jaundice            |                       |                         |                          |         |
| Yes/no                          | 12/72                 | 5/37                    | 7/35                     | 0.533   |
| 1st line regime                 |                       |                         |                          |         |
| GnP/GEM/FFX/GS/S1               | 60/14/6/2/2           | 34/5/1/0/2              | 26/9/5/2/0               | 0.064   |
| 2nd line                        |                       |                         |                          |         |
| Yes/no                          | 63/19                 | 33/8                    | 30/11                    | 0.432   |
| Hb, mg/dl                       |                       |                         |                          |         |
| Median (range)                  | 13.1 (8.1–16.2)       | 13.3 (10.2–15.2)        | 12.8 (8.1–16.2)          | 0.332   |
| Neutrophil-to-lymphocyte ratio  |                       |                         |                          |         |
| Median (range)                  | 2.90 (1.29–13.94)     | 2.73 (1.29–7.55)        | 3.20 (1.72–13.94)        | 0.025   |
| Platelet-to-lymphocyte ratio    |                       |                         |                          |         |
| Median (range)                  | 144.6 (66.4–365.0)    | 132.4 (66.37–289.2)     | 174.6 (77.0–365.0)       | 0.013   |
| mGPS                            |                       |                         |                          |         |
| 0/1–2                           | 67/17                 | 39/3                    | 28/14                    | 0.003   |
| PNI                             |                       |                         |                          |         |
| Median (range)                  | 48.8 (32.1–62.0)      | 50.01 (38.1–56.4)       | 46.9 (32.2–62.0)         | 0.057   |
| Obstructive jaundice            |                       |                         |                          |         |
| Yes/no                          | 12/72                 | 5/37                    | 7/35                     | 0.533   |
bond with inflammation. Furthermore, serum PTX3 was shown to detect bloodstream infection and to predict disease severity by showing a correlation with the Sequential Organ Failure Assessment score.39,40 The elevation in serum PTX3 compared with controls was only seen in stage IV patients with progressive disease, showing its relationship with disease severity. Serum PTX3 successfully indicates the severity of inflammation from local to systemic disease and is a promising marker for cancer cachexia, a paraneoplastic inflammatory syndrome.

Adipose tissues are one of the main targets of cancer cachexia. Cancer cachexia not only induces visceral fat loss but also strongly affects lipid metabolism in adipose tissues. Pancreatic cancer was reported to induce lipolysis in adipose tissues through extracellular vesicles.17 When we examined the expression of characteristic markers of lipid metabolism, including adiponectin, in the periglandal fat of mice with or without orthotopic injection, orthotopic tumors showed dramatically decreased expression of these markers (Figure 1C). This phenomenon was also observed in in vitro coculture experiments with adipose tissue cells and cancer cells (Figure S4A).

### Table 1 (Continued)

| Variable                      | All patients (n = 84) | PTX3 low group (n = 42) | PTX3 high group (n = 42) | p Value |
|-------------------------------|----------------------|-------------------------|--------------------------|---------|
| Amylase, U/L                  |                      |                         |                          |         |
| Median (range)                | 72 (24–697)          | 71.5 (27–697)           | 76 (24–356)              | 0.809   |
| Albumin, g/dl                 |                      |                         |                          |         |
| Median (range)                | 4.1 (2.5–4.8)        | 4.2 (3.4–4.7)           | 4.05 (2.5–4.8)           | 0.035   |
| NEFA, mEq/L                   |                      |                         |                          |         |
| Median (range)                | 0.275 (0.029–0.990)  | 0.277 (0.042–0.896)     | 0.274 (0.028–0.990)      | 0.321   |
| CRP, mg/dl                    |                      |                         |                          |         |
| Yes/no                        | 0.27 (0.04–11.03)    | 0.18 (0.04–1.65)        | 0.49 (0.04–11.03)        | <0.001  |
| HbA1C, percentage             |                      |                         |                          |         |
| Median (range)                | 6.4 (3.3–13.0)       | 6.3 (5.7–12.8)          | 6.4 (3.3–13)             | 0.832   |
| CEA, ng/ml                    |                      |                         |                          |         |
| Median (range)                | 6 (1–1850)           | 4 (1–487)               | 8 (2–1850)               | 0.107   |
| CA19-9, U/ml                  |                      |                         |                          |         |
| Median (range)                | 1128.8 (0.4–94,000)  | 178.4 (0.4–38,746.5)    | 3253.3 (2–940,000)       | 0.001   |
| Pre-SMI, cm²/m²               |                      |                         |                          |         |
| Median (range)                | 39.2 (26.9–57.3)     | 36.8 (26.9–57.3)        | 40.1 (29.3–55.7)         | 0.113   |
| SMI loss/month, %             |                      |                         |                          |         |
| Median (range)                | −0.49 (−25.7–32.3)   | 1.5 (−6.8–32.3)         | −3.4 (−25.7–3.9)         | <0.001  |
| Previsceral fat, cm²          |                      |                         |                          |         |
| Median (range)                | 67.0 (2.19–266.7)    | 60.5 (2.3–225.5)        | 73.26 (2.2–266.7)        | 0.295   |
| Visceral fat loss/month, %    |                      |                         |                          |         |
| Median (range)                | −7.63 (−57.7 to 77.7)| −1.7 (−23.6 to 77.7)    | −15.4 (−57.7 to 31.8)    | <0.001  |
| Presubcutaneous fat, cm²      |                      |                         |                          |         |
| Median (range)                | 88.3 (2.61–208.4)    | 87.3 (7.2–178.4)        | 88.9 (2.6–208.4)         | 0.922   |
| Subcutaneous fat loss/month, %|                      |                         |                          |         |
| Median (range)                | −4.3 (−27.2 to 316.1)| −3.5 (−27.3 to 316.1)   | −4.8 (−25.0 to 292.1)    | 0.871   |

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; FFX, oxaliplatin/irinotecan/fluourouracil/leucovorin; GEM, gemcitabine; GnP, gemcitabine plus nab-paclitaxel; GS, gemcitabine plus S-1; Hb, hemoglobin; HbA1C, hemoglobin A1C; mGPS, modified Glasgow Prognostic Score; NEFA, nonesterified fatty acid; PNI, prognostic nutritional index; SMI, skeletal muscle mass index.
| Variable                       | n   | Univariate analysis |          |          | Multivariate analysis |          |
|-------------------------------|-----|---------------------|----------|----------|-----------------------|----------|
|                               |     | HR  | 95% CI       | p Value   | HR   | 95% CI       | p Value   |
| Sex                           |     |     |              |           |      |              |           |
| Male                          | 43  | 1.07| 0.447–2.578  | 0.874     | 1.00|              |           |
| Female                        | 39  | 1.00|              |           |      |              |           |
| Age                           |     |     |              |           |      |              |           |
| ≥75 years                     | 24  | 2.27| 0.818–6.285  | 0.116     | 1.00|              |           |
| <75 years                     | 58  | 1.00|              |           |      |              |           |
| BMI                           |     |     |              |           |      |              |           |
| ≥21.2                         | 41  | 0.91| 0.381–2.158  | 0.823     | 1.00|              |           |
| <21.2                         | 41  | 1.00|              |           |      |              |           |
| ASA-PS                        |     |     |              |           |      |              |           |
| Class 2–3                     | 48  | 1.11| 0.455–2.685  | 0.825     | 1.00|              |           |
| Class 0–1                     | 34  | 1.00|              |           |      |              |           |
| Tumor size                    |     |     |              |           |      |              |           |
| ≥30mm                         | 47  | 0.54| 0.221–1.342  | 0.187     | 1.00|              |           |
| <30mm                         | 35  | 1.00|              |           |      |              |           |
| Neutrophil-to-lymphocyte ratio|     |     |              |           |      |              |           |
| ≥2.90                         | 40  | 1.86| 0.764–4.512  | 0.172     | 1.00|              |           |
| <2.90                         | 42  | 1.00|              |           |      |              |           |
| Platelet-to-lymphocyte ratio  |     |     |              |           |      |              |           |
| ≥144.6                        | 41  | 0.74| 0.308–1.783  | 0.503     | 1.00|              |           |
| <144.6                        | 41  | 1.00|              |           |      |              |           |
| mGPS                          |     |     |              |           |      |              |           |
| Score 1–2                     | 16  | 4.08| 1.063–15.654 | 0.041     | 1.00|              |           |
| Score 0                       | 66  | 1    |              |           |      |              |           |
| PNI                           |     |     |              |           |      |              |           |
| ≥48.8                         | 41  | 0.49| 0.203–1.202  | 0.120     | 1.00|              |           |
| <48.8                         | 41  | 1.00|              |           |      |              |           |
| Amylase                       |     |     |              |           |      |              |           |
| ≥72 IU/L                      | 41  | 0.74| 0.308–1.783  | 0.503     | 1.00|              |           |
| <72 IU/L                      | 41  | 1.00|              |           |      |              |           |
| Albumin                       |     |     |              |           |      |              |           |
| ≥3.5 g/dl                     | 75  | 0.51| 0.093–2.792  | 0.437     | 1.00|              |           |
| <3.5 g/dl                     | 7   | 1.00|              |           |      |              |           |
| CRP                           |     |     |              |           |      |              |           |
| ≥1.0 mg/dl                    | 16  | 4.08| 1.063–15.654 | 0.041     | 2.01| 0.463–8.734  | 0.351     |
| <1.0 mg/dl                    | 66  | 1.00|              |           |      |              |           |
| HbA1C*                        |     |     |              |           |      |              |           |
| ≥6.5%                         | 34  | 1.83| 0.732–4.594  | 0.196     | 1.00|              |           |
| <6.5%                         | 44  | 1.00|              |           |      |              |           |
| CEA                           |     |     |              |           |      |              |           |
| ≥6 ng/ml                      | 41  | 1.10| 0.460–2.652  | 0.823     | 1.00|              |           |
| <6 ng/ml                      | 41  | 1.00|              |           |      |              |           |
| CA19-9                        |     |     |              |           |      |              |           |
### TABLE 2  (Continued)

| Variable | n   | Univariate analysis | Multivariate analysis |
|----------|-----|---------------------|-----------------------|
|          |     | HR      | 95% CI           | p Value | HR      | 95% CI           | p Value |
| ≥1128 U/ml | 41  | 2.03    | 0.832–4.930      | 0.120   |         |                   |         |
| <1128 U/ml | 41  | 1.00    |                   |         |         |                   |         |
| NEFA     |     |         |                   |         |         |                   |         |
| ≥0.275 mEq/L | 40  | 1.86    | 0.762–4.512      | 0.172   |         |                   |         |
| <0.275 mEq/L | 42  | 1.00    |                   |         |         |                   |         |
| PTX3     |     |         |                   |         |         |                   |         |
| ≥734 ng/ml | 41  | 6.16    | 2.324–16.340     | <0.001  | 5.19    | 1.864–14.455     | 0.002   |
| <734 ng/ml | 41  | 1.00    |                   |         | 1.00    |                   |         |
| Pre-SMI  |     |         |                   |         |         |                   |         |
| ≥39.2 cm²/m² | 42  | 0.99    | 0.411–2.365      | 0.974   |         |                   |         |
| <39.2 cm²/m² | 41  | 1.00    |                   |         |         |                   |         |
| Previsceral fat |     |         |                   |         |         |                   |         |
| ≥67.0 cm² | 40  | 1.86    | 0.764–4.512      | 0.172   |         |                   |         |
| <67.0 cm² | 42  | 1.00    |                   |         |         |                   |         |
| Presubcutaneous fat |     |         |                   |         |         |                   |         |
| ≥76.9 cm² | 40  | 1.24    | 0.515–2.978      | 0.632   |         |                   |         |
| <76.9 cm² | 42  | 1.00    |                   |         |         |                   |         |

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; CRP, C-reactive protein; HbA1C, hemoglobin A1C; HR, hazard ratio; mGPS, modified Glasgow Prognostic Score; NEFA, nonesterified fatty acids; PNI, prognostic nutritional index; PTX3, pentraxin 3; SMI, skeletal muscle mass index.

*Patients without data are excluded.

### TABLE 3  Factors related with skeletal muscle mass index (SMI) loss/month in patients with metastatic pancreatic cancer

| Variable                           | n   | Univariate analysis | Multivariate analysis |
|------------------------------------|-----|---------------------|-----------------------|
|                                    |     | HR      | 95% CI           | p Value | HR      | 95% CI           | p Value |
| Sex                                |     |         |                   |         |         |                   |         |
| Male                               | 43  | 2.43    | 0.998–5.898      | 0.051   |         |                   |         |
| Female                             | 39  | 1       |                   |         |         |                   |         |
| Age                                |     |         |                   |         |         |                   |         |
| ≥75 years                          | 24  | 1.40    | 0.536–3.660      | 0.493   |         |                   |         |
| <75 years                          | 58  | 1       |                   |         |         |                   |         |
| BMI                                |     |         |                   |         |         |                   |         |
| ≥21.2                              | 41  | 0.91    | 0.381–2.158      | 0.825   |         |                   |         |
| <21.2                              | 41  | 1       |                   |         |         |                   |         |
| ASA-PS                             |     |         |                   |         |         |                   |         |
| Class 2–3                          | 48  | 0.79    | 0.327–1.908      | 0.600   |         |                   |         |
| Class 0–1                          | 34  | 1       |                   |         |         |                   |         |
| Tumor size                         |     |         |                   |         |         |                   |         |
| ≥30 mm                             | 47  | 0.72    | 0.298–1.734      | 0.462   |         |                   |         |
| <30 mm                             | 35  | 1       |                   |         |         |                   |         |
| Neutrophil-to-lymphocyte ratio     |     |         |                   |         |         |                   |         |
| ≥2.90                              | 40  | 1.82    | 0.755–4.365      | 0.183   |         |                   |         |
| <2.90                              | 42  | 1       |                   |         |         |                   |         |

Platelet-to-lymphocyte ratio

(Continues)
| Variable      | n  | Univariate analysis |                           | Multivariate analysis |
|--------------|----|---------------------|---------------------------|-----------------------|
|              |    | HR                  | 95% CI                    | p Value               |
|              |    |                     |                           |                       |
| ≥144.6       | 41 | 1.34                | 0.563–3.200               | 0.508                 |
| <144.6       | 41 | 1                   |                           |                       |
| mGPS         |    |                     |                           |                       |
| Score 1–2    | 16 | 3.39                | 0.990–11.594              | 0.052                 |
| Score 0      | 66 | 1                   |                           |                       |
| PNI          |    |                     |                           |                       |
| ≥48.8        | 41 | 0.61                | 0.255–1.465               | 0.270                 |
| <48.8        | 41 | 1                   |                           |                       |
| Amylase      |    |                     |                           |                       |
| ≥72 IU/L     | 41 | 0.91                | 0.381–2.158               | 0.825                 |
| <72 IU/L     | 41 | 1                   |                           |                       |
| Albumin      |    |                     |                           |                       |
| ≥3.5 g/dl    | 75 | 0.41                | 0.075–2.251               | 0.305                 |
| <3.5 g/dl    | 7  | 1                   |                           |                       |
| CRP          |    |                     |                           |                       |
| ≥1.0 mg/dl   | 16 | 3.39                | 0.990–11.594              | 0.052                 |
| <1.0 mg/dl   | 66 | 1                   |                           |                       |
| HbA1C*       |    |                     |                           |                       |
| ≥6.5%        | 34 | 2.41                | 0.959–6.067               | 0.061                 |
| <6.5%        | 44 | 1                   |                           |                       |
| CEA          |    |                     |                           |                       |
| ≥6 ng/ml     | 41 | 0.91                | 0.381–2.158               | 0.907                 |
| <6 ng/ml     | 41 | 1                   |                           |                       |
| CA19-9       |    |                     |                           |                       |
| ≥1128 U/ml   | 41 | 1.63                | 0.682–3.915               | 0.270                 |
| <1128 U/ml   | 41 | 1                   |                           |                       |
| NEFA         |    |                     |                           |                       |
| ≥0.275 mEq/L| 40 | 1.22                | 0.513–2.912               | 0.651                 |
| <0.275 mEq/L| 42 | 1                   |                           |                       |
| PTX3         |    |                     |                           |                       |
| ≥734 ng/ml   | 41 | 9.70                | 3.525–26.677              | <0.001                |
| <734 ng/ml   | 41 | 1                   |                           |                       |
| Pre-SMI      |    |                     |                           |                       |
| ≥39.2 cm²/m²| 42 | 2.70                | 1.105–6.599               | 0.029                 |
| <39.2 cm²/m²| 40 | 1                   |                           |                       |
| Previsceral fat |   |                     |                           |                       |
| ≥67.0 cm²   | 40 | 1.82                | 0.755–4.365               | 0.183                 |
| <67.0 cm²   | 42 | 1                   |                           |                       |
| Presubcutaneous fat |   |                     |                           |                       |
| ≥76.9 cm²   | 40 | 0.68                | 0.284–1.621               | 0.383                 |
| <76.9 cm²   | 42 | 1                   |                           |                       |

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carinoembryonic antigen; CI, confidence interval; CRP, C-reactive protein; HbA1C, hemoglobin A1C; HR, hazard ratio; mGPS, modified Glasgow Prognostic Score; NEFA, nonesterified fatty acid; PNI, prognostic nutritional index; PTX3, pentraxin 3.

*Patients without data are excluded.
### Table 4: Prognostic factors for metastatic pancreatic cancer

| Variable                  | Univariate analysis | Multivariate analysis |
|---------------------------|---------------------|-----------------------|
|                           | n       | HR  | 95% CI   | p Value | HR   | 95% CI   | p Value |
| **Sex**                   |         |     |          |         |      |          |         |
| Male                      | 45      | 1.08| 0.697–1.675| 0.731   |       |          |         |
| Female                    | 39      | 1   |          |         |      |          |         |
| **Age**                   |         |     |          |         |      |          |         |
| ≥75 years                 | 24      | 1.55| 0.959–2.515| 0.073   |       |          |         |
| <75 years                 | 60      | 1   |          |         |      |          |         |
| **BMI**                   |         |     |          |         |      |          |         |
| ≥21.2                     | 42      | 1.03| 0.666–1.597| 0.891   |       |          |         |
| <21.2                     | 42      | 1   |          |         |      |          |         |
| **ASA-PS**                |         |     |          |         |      |          |         |
| Class 2-3                 | 50      | 0.95| 0.612–1.484| 0.831   |       |          |         |
| Class 0-1                 | 34      | 1   |          |         |      |          |         |
| **Tumor size**            |         |     |          |         |      |          |         |
| ≥30mm                     | 36      | 1.07| 0.679–1.681| 0.776   |       |          |         |
| <30mm                     | 48      | 1   |          |         |      |          |         |
| **Neutrophil-to-lymphocyte ratio** | |     |          |         |      |          |         |
| ≥2.90                     | 42      | 1.53| 0.988–2.383| 0.057   |       |          |         |
| <2.90                     | 42      | 1   |          |         |      |          |         |
| **Platelet-to-lymphocyte ratio** | |     |          |         |      |          |         |
| ≥144.6                    | 42      | 1.07| 0.693–1.663| 0.751   |       |          |         |
| <144.6                    | 42      | 1   |          |         |      |          |         |
| **mGPS**                  |         |     |          |         |      |          |         |
| Score 1-2                 | 17      | 3.32| 1.875–5.886| <0.001  |       |          |         |
| Score 0                   | 67      | 1   |          |         |      |          |         |
| **PNI**                   |         |     |          |         |      |          |         |
| ≥48.8                     | 42      | 0.63| 0.407–0.985| 0.043   | 0.77  | 0.468–1.252| 0.288  |
| <48.8                     | 42      | 1   |          |         |      | 1          |         |
| **Amylase**               |         |     |          |         |      |          |         |
| ≥72 IU/L                  | 42      | 0.87| 0.561–1.361| 0.552   |       |          |         |
| <72 IU/L                  | 42      | 1   |          |         |      |          |         |
| **Albumin**               |         |     |          |         |      |          |         |
| ≥3.5 g/dl                 | 77      | 0.29| 0.132–0.653| 0.003   | 0.61  | 0.248–1.488| 0.276  |
| <3.5 g/dl                 | 7       | 1   |          |         |      | 1          |         |
| **CRP**                   |         |     |          |         |      |          |         |
| ≥1.0 mg/dl                | 17      | 3.32| 1.875–5.886| <0.001  | 2.02  | 1.033–3.953| 0.040  |
| <1.0 mg/dl                | 67      | 1   |          |         |      | 1          |         |
| **HbA1C***                |         |     |          |         |      |          |         |
| ≥6.5%                     | 36      | 1.36| 0.861–2.141| 0.188   |       |          |         |
| <6.5%                     | 44      | 1   |          |         |      |          |         |
| **CEA**                   |         |     |          |         |      |          |         |
| ≥6 ng/ml                  | 42      | 1.48| 0.948–2.314| 0.084   |       |          |         |
| <6 ng/ml                  | 42      | 1   |          |         |      |          |         |

(Continues)
have cancer cachexia with predicted loss of muscle mass and visceral fat and might not have multiple chances for chemotherapy induction.

**AUTHOR CONTRIBUTIONS**
KS, HH, and TTak designed, analyzed, and drafted the work. MS, SKat, YS, MF, and SKud significantly contributed in data analysis and data collection. YS, KF, KShir, YM, SS, and KM contributed in interpretation of the results. TY, AN, TK, RS, and TTat contributed in study design and data interpretation. All authors reviewed the manuscript and revised it critically on intellectual content. All authors approved the final version of the manuscript to be published.

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**DISCLOSURE**
The authors have no conflict of interest to declare.

**APPROVAL OF THE RESEARCH PROTOCOL**
This study followed the Declaration of Helsinki and was approved by the Institutional Review Board of Osaka University (approval no. 17160).

**INFORMED CONSENT**
All patients enrolled provided written informed consent and agreed to preserve serum before treatment.

**REGISTRY AND REGISTRATION NO. OF THE STUDY/TRIAL**
N/A.

**ANIMAL STUDIES**
All measures possible were taken to lessen suffering. All animal experiments were approved by the institutional committee (approval no. 30-015) and carried out according to the approved protocol.

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