



Original research

Clinical impact of sarcopenia on prognosis in pancreatic ductal adenocarcinoma: A retrospective cohort study



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HIGHLIGHTS

- Skeletal muscle index was measured in pancreatic ductal adenocarcinoma patients by using preoperative computed tomography.
- Low-skeletal muscle index was an independent prognostic factor for overall survival in patients with Body mass index ≥ 22 .
- Body mass index and visceral fat area was not associated with prognosis.
- Computed tomography is a simple and useful tool for predicting prognosis.

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ABSTRACT

Objectives: To investigate the impact of the body composition such as skeletal muscle, visceral fat and body mass index (BMI) on patients with resected pancreatic ductal adenocarcinoma (PDAC).

Methods: A total of 265 patients who underwent curative surgery for PDAC were examined in this study. The total skeletal muscle and fat tissue areas were evaluated in a single image obtained at the third lumbar vertebra during a preoperative computed tomography (CT) scan. The patients were assigned to either the sarcopenia or non-sarcopenia group based on their skeletal muscle index (SMI) and classified into high visceral fat area (H-VFA) or low VFA (L-VFA) groups. The association of clinicopathological features and prognosis with the body composition were statistically analyzed.

Results: There were 170 patients (64.2%) with sarcopenia. The median survival time (MST) was 23.7 months for sarcopenia patients and 25.8 months for patients without sarcopenia. The MST was 24.4 months for H-VFA patients and 25.8 months for L-VFA patients. However, sarcopenia patients with BMI ≥ 22 exhibited significantly poorer survival than patients without sarcopenia (MST: 19.2 vs. 35.4 months, $P = 0.025$). There was a significant difference between patients with and without sarcopenia who did not receive chemotherapy (5-year survival rate: 0% vs. 68.3%, $P = 0.003$). The multivariate analysis revealed that tumor size, positive dissected peripancreatic tissue margin, and sarcopenia were independent prognostic factors.

Conclusions: Sarcopenia is an independent prognostic factor in PDAC patients with a BMI ≥ 22 . Therefore, evaluating skeletal muscle mass may be a simple and useful approach for predicting patient prognosis.

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) continues to have the worst prognosis of all the gastrointestinal malignancies despite the recent development of several preoperative and postoperative treatments [1]. A complete surgical resection offers the only

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possibility of cure. However, less than 20% of patients have localized and potentially curable tumors at the time of diagnosis, and considerable advances in diagnostic techniques are required [2,3]. As a result, only moderate improvements in patient outcomes have been achieved.

Previous studies have identified prognostic factors, including both pancreatic cancer-specific clinicopathological factors and individual patient characteristics. Factors such as weight loss, muscle wasting, and cachexia are hallmarks of PDAC that may be associated with the depletion of both skeletal muscle and adipose tissue [4–6]. Sarcopenia is defined as the degenerative loss of skeletal muscle mass that is quantifiable using cross-sectional imaging computed tomography (CT) measurements of psoas area and muscle density [7]. Visceral adipose tissue loss is also associated with poor survival in pancreatic cancer patients [8]. Cumulatively, these findings suggest that the characterization of changes in the composition of various body compartments may provide important prognostic information for patients with PDAC.

Previous studies have demonstrated that up to 50% of patients with advanced cancer have frank sarcopenia [9,10]. Although only a few studies have examined the association between the presence of sarcopenia and outcomes following surgery, these studies have demonstrated that sarcopenia is associated with poor survival in patients undergoing surgery for melanoma, colorectal liver metastasis, liver transplantation, and pancreatic cancer [11–15]. Therefore, it is important to identify useful prognostic factors and individual patient characteristics to determine the best therapeutic approach in each case. However, the impact of sarcopenia on overall survival in PDAC remains unclear.

The aim of this study was to identify the impact of the body composition such as skeletal muscle, visceral fat, and BMI in patients undergoing resection for PDAC and to investigate the relationship between various body composition characteristics, clinical factors, and outcomes of patients with PDAC.

2. Materials and methods

2.1. Patients

Two hundred and sixty-five patients who underwent surgery with curative intent for PDAC between May 2005 and November 2014 in the Department of Gastroenterological Surgery, Nagoya University Hospital were recruited. All patients were confirmed to have a histological diagnosis of PDAC. A total of 187 patients underwent pancreaticoduodenectomy, and 60 patients underwent distal pancreatectomy. 18 patients underwent total pancreatectomy. Pancreatectomy and systematic lymphadenectomy were performed with curative intent in all patients. We excluded patients for the following reasons: received neoadjuvant chemoradiation therapy ($n = 41$), and underwent middle pancreatectomy due to different preoperative diagnosis ($n = 1$). Conversely, we included patients as follows: diagnosed as having distant metastasis during surgery ($n = 22$), and surgical death ($n = 2$).

All patients were evaluated for the expression of CA19-9 and examined by CT every 6 months after discharge. 164 patients had recurrence, and the breakdowns are as follows: liver recurrence ($n = 2$), local recurrence ($n = 42$), peritoneal recurrence ($n = 34$), lymph node recurrence ($n = 22$), lung recurrence ($n = 8$), remnant pancreas recurrence ($n = 4$), and bone recurrence ($n = 2$).

The median follow-up duration was 16.3 months (range, 0.4–107.7 months). A total of 174 patients were treated with adjuvant chemotherapy (gemcitabine and/or S-1, oral 5-fluorouracil prodrug tegafur with oteracil, and gimeracil). Gemcitabine was administered at a dose of 1000 mg/m² weekly for 3 weeks, followed by 1 week of withdrawal. Oral S-1 was

administered at a dose of 80 mg/m² from days 1–14, followed by a 1-week withdrawal period. All chemotherapy treatments were initiated within 2 months of surgery in eligible patients, and the treatment continued for a minimum of 6 months. Written informed consent for inclusion in the study, as required by the Institutional Review Board of Nagoya University, was obtained from all patients.

2.2. Image analysis

All patients underwent preoperative abdominal CT within 30 days of surgery. The total skeletal muscle and fat tissue area (cm²) were evaluated in a single image at the 3rd lumbar vertebra (L3) using Hounsfield unit thresholds of –29 to +150 for skeletal muscle and –200 to –50 for visceral and subcutaneous fat tissues. The preoperative CT images were used for all assessments. All CT images were analyzed using SYNAPSE VINCENT software version 4.0 (Fuji Film, Tokyo, Japan). The cross-sectional skeletal muscle area (cm²) was normalized by the square of the height (m²) to obtain the L3 skeletal muscle index (SMI, cm²/m²). The cut-off values for skeletal muscle were defined as 43.75 cm²/m² for men and 38.5 cm²/m² for women [16]. The cut-off values for visceral fat area (VFA) were defined as 103 cm² for men and 69.0 cm² for women. These values are associated with metabolic abnormalities in Japan [17]. These cut-off values were used to assign patients to the sarcopenia or non-sarcopenia groups and the high VFA (H-VFA) or low VFA (L-VFA) groups.

2.3. Statistical analysis

All differences in the numerical data between groups were evaluated using Fisher's exact test or the χ^2 test. The patient overall survival rates were calculated using the Kaplan-Meier method. The difference in survival curves was analyzed using the log-rank test. The independent prognostic factors were analyzed with a Cox proportional hazards regression model. All data are expressed as the means \pm SD. The presence of a statistically significant difference was denoted by $P < 0.05$. The data were analyzed using JMP version 10 software (JMP, SAS Institute, Cary, NC).

3. Results

3.1. Patient demographics

The clinical and pathological characteristics of the 265 patients included in this study are shown in Table 1. The average patient age in this study population was 65.4 years. There were 164 (62%) male patients and 101 (38%) female patients. The tumor was located at the head of the pancreas in 198 patients. The tumor was larger than 2 cm in diameter in the majority of patients (74.7%). The pathological analysis indicated that 62.6% of patients had lymph node metastasis. Additionally, portal vein invasion was observed in 40.0% of the patients. There were 145 patients (54.7%) with postoperative complications \geq Clavien-Dindo II. There were no deaths within 90 days of resection.

The average SMI was 40.2 cm²/m² after normalizing by patient height. The SMI was significantly higher in males than females (43.6 vs. 34.6 cm²/m², $P < 0.001$). The SMI and VFA values in the high BMI (≥ 22) group were significantly higher than those in the low BMI (< 22) group regardless of gender. The average VFA and Subcutaneous fat area (SFA) were significantly different between male and female patients (105.3 vs. 71.9 cm², $P < 0.001$, 69.0 vs. 93.6 cm², $P < 0.001$; Table 1).

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