Impact of skeletal muscle mass on the prognosis of patients undergoing neoadjuvant chemotherapy for resectable or borderline resectable pancreatic cancer

Hiroki Nakajima, PT[a, b], Junpei Yamaguchi, MD [a], Hideki Takami, MD[c], Masamichi Hayashi, MD[c], Yasuhiro Kodera, MD[c], Yoshihiro Nishida, MD[b], Nobuyuki Watanabe, MD[a], Shunsuke Onoe, MD[a], Takashi Mizuno, MD[a], Yukihiro Yokoyama, MD[a], Tomoki Ebata, MD[a],

[a]Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

[b]Department of Rehabilitation, Nagoya University Hospital, Nagoya, Japan

[c]Department of Gastroenterological Surgery (Surgery II), Nagoya, Japan.

Corresponding author: Yukihiro Yokoyama, MD

Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of Medicine

65 Tsurumai-cho, Showaku, Nagoya, Aichi 466-8550, Japan.

Tel.: +81 52 744 2222

E-mail: yyoko@med.nagoya-u.ac.jp

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ABSTRACT

Background: Neoadjuvant chemotherapy is a common therapeutic procedure for patients with pancreatic cancer. This study aimed to investigate the association between the total psoas area (TPA) and prognosis in patients undergoing neoadjuvant chemotherapy for resectable or borderline resectable pancreatic cancer.

Study Design: This retrospective study included patients who underwent neoadjuvant chemotherapy for pancreatic cancer. TPA was measured at the level of the L3 vertebra using computed tomography. The patients were divided into low-TPA and normal-TPA groups. These dichotomizations were separately performed in patients with resectable and those with borderline resectable pancreatic cancer.

Results: In total, 44 patients had resectable pancreatic cancer and 71 patients had borderline resectable pancreatic cancer. Overall survival among patients with resectable pancreatic cancer did not differ between the normal- and low-TPA groups (median, 19.8 vs. 21.8 months, p=0.447), whereas among patients with borderline resectable pancreatic cancer, the low-TPA group had shorter overall survival than the normal-TPA group (median, 21.8 vs. 32.9 months, p<0.006). Among patients with borderline resectable pancreatic cancer, the low-TPA group was predictive of poor overall survival (adjusted hazard ratio, 2.57, p=0.037).

Conclusions: Low-TPA is a risk factor of poor survival in patients undergoing neoadjuvant chemotherapy for borderline resectable pancreatic cancer. TPA evaluation could potentially suggest the treatment strategy in this disease.

Keywords: Sarcopenia, Psoas muscles, Neoadjuvant chemotherapy, Pancreatectomy, Prognosis

INTRODUCTION

Surgical resection is the only potentially curative treatment option for pancreatic cancer. However, unfavorable outcomes are commonly observed even after aggressive surgery due to a high recurrence rate [1]. Neoadjuvant chemotherapy has been used in patients with borderline resectable pancreatic cancer to improve their probability of survival [2]. Additionally, a recent Japanese report confined to resectable tumors demonstrated that patients treated with neoadjuvant chemotherapy had significantly longer survival than those who were not administered such treatment [3]. Therefore, currently, chemotherapy is generally considered before resection of pancreatic cancer irrespective of whether the tumor is resectable or borderline resectable.

A major issue in patients undergoing neoadjuvant chemotherapy is heterogeneous response to treatment. Poor response to chemotherapy precludes the intended curative resection and results in poor long-term overall survival (OS). In a previous study, the resection rate of patients with resectable or borderline resectable pancreatic cancer who were treated with neoadjuvant therapy was 72% [4]. Severel chemotherapy-induced adverse events that deteriorate the patients' quality of life are also serious problems. Therefore, it is important to determine whether neoadjuvant chemotherapy may be beneficial to a patient at the initial presentation.

Several investigators have observed that preoperative skeletal muscle loss deteriorated the postoperative outcomes and decreased the long-term survival of patients with pancreatic cancer [5,6]. Although only a few recent studies have reported that skeletal muscle mass loss before neoadjuvant chemotherapy is associated with decreased survival [7,8], the prognostic impact of skeletal muscle mass based on resectability classification remains unknown. It may also be more suitable for patients with resectable pancreatic cancer and those with borderline resectable pancreatic cancer to be considered separately because of

their different anatomic tumor stages, cachexia, and nutritional status.

This study investigated the impact of skeletal muscle mass as a simple biophysical marker for predicting the prognosis of patients with resectable or borderline resectable pancreatic cancers while undergoing neoadjuvant chemotherapy

METHODS

Patients

This retrospective study analyzed data of patients who were treated with neoadjuvant chemotherapy for resectable or borderline resectable pancreatic cancers between January 2015 and September 2020 at Nagoya University Hospital. Patients who were treated with combined radiation therapy or had previously received chemotherapy in another hospital were excluded. The Institutional Review Board of Nagoya University Hospital approved this study (approval no. 20774), which was performed in line with the tenets of the Declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. The need for informed consent was waived due to the retrospective nature of the study. However, the study protocol was public and the participants had the right to refuse to participate in this study.

Clinical variable data collection

Classification of resectability was based on the National Comprehensive Cancer Network guidelines® for pancreatic adenocarcinoma definitions. All classifications were performed by the expert radiologists in Nagoya University Hospital. Demographic data, including age, sex, height, body weight, body mass index (BMI), tumor location, and comorbidities were recorded. The Charlson Comorbidity Index was used to uniformly score comorbid conditions [9]. Prognostic scores, including the prognostic nutritional index (PNI), modified Glasgow Prognostic Score (mGPS), C-reactive protein-to-albumin ratio, neutrophil-

to-lymphocyte ratio, and platelet-to-lymphocyte ratio were calculated before neoadjuvant chemotherapy. The PNI was calculated using the following equation: PNI = 10 × serum albumin (g/dL) + 0.005 × total peripheral blood lymphocyte count (/mm^3) [10]. The mGPS was evaluated as previously described [11]. Briefly, patients with elevated C-reactive protein (>1.0 mg/dL) and low albumin (<3.5 g/dL) levels were assigned a score of 2, patients with only one of these biochemical abnormalities were assigned a score of 1, and patients with no such abnormalities were assigned a score of 0.

Tumor size was measured on computed tomography images that were acquired before and after neoadjuvant chemotherapy and the response rate was evaluated according to the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, Version 1.1[12]. Serum carbohydrate antigen 19-9 (CA19-9) levels were evaluated before and after neoadjuvant chemotherapy. The chemotherapy regimen included a combination of fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX); gemcitabine plus nab-paclitaxel; gemcitabine plus S-1; or S-1, and was selected at the physician's discretion. Patients with resectable pancreatic cancer underwent two courses of gemcitabine plus S-1. In contrast, patients with borderline resectable pancreatic cancer underwent four courses of FOLFIRINOX or two courses of gemcitabine plus nab-paclitaxel based on a protocol of clinical study performed in the authors' institution [13]. All regimens continued for 2 months, and the outcomes of chemotherapy were evaluated. If the tumor is resectable at this point, patients underwent surgery.

The duration of chemotherapy and the relative dose intensity were recorded. The chemotherapy completion rate (dose-limiting toxicity) was defined as the need to reduce the dose of the drug, delay its administration, or discontinue the protocol [14]. Hematotoxicity was assessed using the Common Terminology Criteria for Adverse Events, Version 4.0. The rate of achievement of pancreatic resection after the administration of neoadjuvant

chemotherapy was recorded. Intra-operative data, such as operative procedure, operation time, and intraoperative blood loss were also recorded. Pathologic findings were assessed based on the Evans system, which is a 4-tiered scoring according to the percentage of residual viable neoplastic cells in the tumor after therapy [15]. At Grade I, 0–9% of the tumor cells were destroyed; Grade IIa, 10–50% of the tumor cells were destroyed; Grade IIb, 51–90% of the tumor cells were destroyed; Grade III, <10% of the tumor cells were present; and Grade IV, no viable tumor cells were observed.

The severity of postoperative complications was classified using the Clavien-Dindo classification system [16]. A major complication was defined as a complication with Clavien grade ≥3. Patients were treated with adjuvant chemotherapy, which included gemcitabine or S-1 unless contraindicated in a given patients. OS was the primary endpoint of this study. The time to the endpoint was calculated as the number of days from starting treatment to the event date. Recurrence-free survival (RFS) was also evaluated in this study. The time to the endpoint was calculated as the number of days from starting operative date to the event date.

Evaluation of muscle mass and definition of low skeletal muscle mass

The total psoas muscle area (TPA), an index of skeletal muscle mass, was assessed using abdominal/pelvic computed tomography images acquired before neoadjuvant chemotherapy. As described before, TPA was measured at the third lumbar vertebra level on the first image in which both vertebral spines were visible [17,18]. The measurements were done semi-automatically using the SYNAPSE VINCENT software (Fujifilm Medical Co., Ltd., Tokyo, Japan). A range of -29 to 150 Hounsfield units (HU) were set to calculate the skeletal muscle cross section. The TPA (cm^2) was divided by the patient height squared (m^2) for normalization. Patients with the lowest tertile of the normalized TPA in each sex were categorized as the low-TPA group whereas others were categorized as the normal-TPA group [19,20]. These dichotomizations were separately performed in the patients with resectable

and those with borderline resectable pancreatic cancer.

Statistical analysis

Data for continuous variables are expressed as the median and interquartile range (IQR). Categorical variables are expressed as numbers and percentages. The cohort was divided into resectable and borderline resectable pancreatic cancer, which were separately analyzed. Differences between the normal-TPA and low-TPA groups were analyzed using the χ^2 or Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables.

Survival curves were estimated using the Kaplan–Meier method, and differences were assessed using the log-rank test. Age, sex, and BMI before neoadjuvant chemotherapy were selected as adjustment variables in multivariate Cox regression analyses for OS and RFS because these factors were shown to have a prognostic impact in previous studies [21]. Hazard ratios (HR) are reported with the corresponding 95% confidence intervals (CI). All analyses were conducted using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). A two-tailed $p<0.05$ was considered statistically significant.

RESULTS

Participants

This study assessed the data of 187 patients treated with neoadjuvant chemotherapy for resectable or borderline resectable pancreatic cancer, of which 72 were excluded as they had received radiation therapy ($n = 61$) or chemotherapy in a previous hospital ($n = 11$). The remaining 115 patients were included in the analysis (Fig. 1). There were 44 patients with resectable pancreatic cancer and 71 patients with borderline resectable pancreatic cancer.

Characteristics of patients with resectable pancreatic cancer

Table 1 summarizes the characteristics of patients with resectable pancreatic cancer.

The median (IQR) age at diagnosis was 72 (65–76) years and the median BMI was 20.8 (19.4–23.1) kg/m^2. The median (IQR) normalized TPA was 8.24 (7.70–9.60) cm^2/m^2 for male patients and 6.26 (5.61–6.82) cm^2/m^2 for female patients. The cutoff values for the low-TPA group were 7.79 cm^2/m^2 in male patients and 5.70 cm^2/m^2 in female patients; all patients with TPA above these values were included in the normal-TPA group. The normal- and low-TPA groups were comparable for age, sex, height, body weight, tumor location, Charlson Comorbidity Index, prognostic scores, and the serum levels of CA 19-9. Patients in the low-TPA group had significantly lower body mass index and smaller tumor size than those in the normal-TPA group. The selected chemotherapy regimen was predominantly gemcitabine + S-1 in both groups. Patients in the low-TPA group had a significantly shorter duration of chemotherapy, lower relative dose intensity, and lower rate of chemotherapy completion than those in the normal-TPA group. The changes in tumor size (0 vs. –5 mm, p=0.008) after neoadjuvant chemotherapy were significantly lower in patients in the low-TPA than those in the normal-TPA group. Response rate according to the RECIST criteria and adverse events during chemotherapy did not differ between the normal- and low-TPA groups. The resection completion rate of pancreatic cancer was 100% in both groups. The type of procedure performed, combined resections, operation time, blood loss, Evans grading, the incidence of major postoperative complications (Clavien-Dindo grade ≥3), length of postoperative hospital stay, and the proportion of patients who received adjuvant chemotherapy did not differ between the two groups. The rate of R0 resection was favorable and was not significantly different between the normal-TPA and low-TPA groups (90% vs. 93%, p=1.000).

Characteristics of borderline resectable pancreatic cancer

Table 2 summarizes the characteristics of borderline resectable pancreatic cancer. The median (IQR) age at diagnosis was 67 (60–72) years and the median BMI was 21.3 (19.6–23.3) kg/m^2. The median (IQR) normalized TPA was 7.54 (6.93–8.92) cm^2/m^2 for male

patients and 7.03 (6.20–7.53) cm^2/m^2 for female patients. The cut-off value for the low-TPA group was 7.16 cm^2/m^2 in male patients and 6.44 cm^2/m^2 in female patients; all patients with TPA above these values were included in the normal-TPA group. The normal- and low-TPA groups were comparable for age, sex, height, body weight, tumor location, Charlson Comorbidity Index, prognostic scores, tumor size, and serum levels of CA 19-9. Patients with low TPA had significantly lower body mass index than those with normal TPA. Regarding the regimen, most of the patients received gemcitabine + nab-paclitaxel in the low-TPA group, whereas FOLFIRINOX was selected more often in the normal-TPA group. The two groups were similar in terms of chemotherapy. Patients in the low-TPA group had a significantly lower relative dose intensity than those in the normal-TPA group. The chemotherapy completion rate was significantly lower in the low-TPA group than in the normal-TPA group (39% vs. 81%, p=0.001). The resection completion rate of pancreatic cancer was 87%. It was significantly lower in the low-TPA group than in the normal-TPA group (70% vs. 96%, p=0.004) (Fig. 2). The change of tumor size, response rate according to the RECIST criteria, adverse events, the type of performed operation, combined resection, operation time, blood loss, Evans grading, the incidence of major postoperative complications (Clavien-Dindo grade ≥3), length of postoperative hospital stay, and adjuvant chemotherapy did not differ between the two groups. The rate of R0 resection was significantly lower in the low-TPA group than in the normal-TPA group (39% vs.79%, p=0.046).

Impact of skeletal muscle mass before neoadjuvant chemotherapy on the prognosis

In patients with resectable pancreatic cancer, the median (IQR) follow-up period was 1.7 (1.3–2.0) years, and a total of 9 (20.5 %) patients died. Kaplan–Meier curves indicated that the OS was not significantly different between the normal- and low-TPA groups (median, 19.8 vs. 21.8 months; Log-rank, p=0.447) (Fig. 3A). In addition, the RFS was not

significantly different between the normal- and low-TPA groups (median, 13.8 vs. 18.0 months; Log-rank, p=0.064) (Supplementary Fig. 2A). In patients with borderline resectable pancreatic cancer, the median (IQR) follow-up period was 2.2 (1.5–3.4) years, and a total of 25 (35.2 %) patients died. Kaplan–Meier curves indicated that the OS was significantly shorter in the low-TPA group compared to OS in the normal-TPA group (median, 21.8 vs. 32.9 months; Log-rank, p<0.006) (Fig. 3B). The RFS was not significantly different between the normal- and low-TPA groups (median, 18.4 vs. 13.8 months; Log-rank, p=0.147) (Supplementary Fig. 2B). After adjusting for possible confounding factors, the risk of mortality was higher in the low-TPA group than in the normal-TPA group (adjusted HR, 2.57; 95% CI, 1.06–6.24; p=0.037) (Table 3).

DISCUSSION

This study had several key findings. First, in patients with pancreatic cancer who received neoadjuvant chemotherapy, TPA prior to treatment had a different prognostic impact depending on the resectability of the tumor. Low TPA before neoadjuvant chemotherapy was a significant prognostic factor in patients with borderline resectable pancreatic cancer, whereas it was not significant in patients with resectable pancreatic cancer. Second, the relative dose intensity and the chemotherapy completion rate were lower in patients with low TPA regardless of resectability classification. These observations clearly showed the importance of skeletal muscle mass before neoadjuvant chemotherapy in patients with pancreatic cancer.

A number of previous studies showed that preoperative muscle mass loss has adverse effects on the prognosis of patients undergoing pancreatic resection for pancreatic cancer [5,22]. However, few reports have evaluated the impact of muscle mass loss in patients undergoing neoadjuvant chemotherapy for pancreatic cancer [8,7,23,18]. In this study,

patients who had resectable or borderline resectable pancreatic cancers and received neoadjuvant chemotherapy were separately analyzed to identify the impact of muscle mass loss on the chemotherapy completion rate, resection completion rate, R0 resection rate, and long-term survival. To the best of our knowledge, this is the first report that performed this type of analysis.

Among patients who undergo neoadjuvant chemotherapy, some patients may drop out of the resection protocol because of severe adverse events or disease progression during treatment. Therefore, it is critical to identify patients who may benefit from neoadjuvant chemotherapy before commencing treatment. This study demonstrated that low TPA prior to neoadjuvant chemotherapy was an independent predictor of poor prognosis in patients with borderline resectable pancreatic cancer. In contrast, low TPA did not have an impact on the prognosis of patients with resectable pancreatic cancer. These results may be partly attributed to the differences in tumor status, extent of cachexia, and malnutrition between patients with borderline resectable pancreatic cancer and those with resectable pancreatic cancer. In fact, TPA was lower in patients with borderline resectable pancreatic cancer than in those with resectable pancreatic cancer. Our results suggest that in patients with borderline resectable pancreatic cancer who are required to undergo neoadjuvant chemotherapy, to minimize the detrimental effects of chemotherapy, the muscle mass of these patients should be considered in order to select the appropriate chemotherapy regimen and its dose intensity.

Is it possible to improve the nutritional status or increase muscle mass in patients with cancer? A previous study from our institution indicated that a prehabilitation program (nutritional and exercise therapy) increased the 6-minute walking distance and PNI, and serum albumin levels, even in patients with hepato-pancreato-biliary malignancy [24]. Furthermore, the skeletal muscle mass also increased, and total body fat decreased in patients treated with this prehabilitation program. Although this study has only included patients

undergoing upfront surgery without neoadjuvant chemotherapy, the prehabilitation program might also be useful for patients with pancreatic cancer who are undergoing chemotherapy. Based on this hypothesis, the benefit of the prehabilitation program in patients undergoing neoadjuvant chemotherapy for hepato-pancreato-biliary malignancy is being investigated in an ongoing clinical trial at our institution (Registration, UMIN000038791; institutional review board approval number, 2018-0369).

In this study, the relative dose intensity and the rate of chemotherapy completion were lower in patients with low TPA both among patients with resectable pancreatic cancer and those with borderline resectable pancreatic cancer. The pathophysiological mechanism that explains the association between muscle mass and the response to chemotherapy remains unclear. In recent years, the relationships between muscle strength, muscle mass, and physical activity and immune function have been demonstrated [25-27]. Narsale et al. reported correlations between T cell population levels and muscle strength, physiological performance, and body composition in patients with cancer [26]. These results imply that the immune response to cancer cells may be different between patients with normal and low skeletal muscle masses. Another report from our institution demonstrated that the changes in lymphocyte count during the waiting period for surgery were positively proportional to the average daily steps per day, which is an indicator of physical activity [28]. These results indirectly suggested an association between skeletal muscle mass (or physiological activity) and immune function (including cancer resistance). Further mechanistic investigation is necessary to clarify the association between the skeletal muscle mass and immune response to cancer.

This study had several limitations. First, this was a retrospective, single-institution study with a small number of patients and a short follow-up period. Second, the study population included only Asian patients with pancreatic cancer, and a low skeletal muscle

mass was defined as the lowest normalized sex-specific TPA tertile [19,20]. Cut-off values have not yet been established in the category of surgery for pancreatic cancer. An exact definition of low skeletal muscle mass that could be used worldwide is necessary to further assess the importance of low skeletal muscle mass in patients with pancreatic cancer. Third, the chemotherapeutic regimen was selected depending on the physicians' discretion and the impact of different regimens on prognosis was not analyzed because of the low number of patients in each regimen. Ideally, the treatment response should be evaluated using a uniform chemotherapy regimen. To overcome these limitations, further large-scale prospective studies are necessary to determine the importance of skeletal muscle mass in patients undergoing neoadjuvant chemotherapy for pancreatic cancer.

CONCLUSIONS

Although low skeletal muscle mass prior to neoadjuvant chemotherapy was not associated with prognosis in patients with resectable pancreatic cancer, it was significantly associated with poor prognosis in patients with borderline resectable pancreatic cancer. The evaluation of muscle mass before neoadjuvant chemotherapy could be a predictive biomarker for prognosis in patients with borderline resectable pancreatic cancer. Maintaining muscle mass before and during chemotherapy in patients with pancreatic cancer may be important for favorable outcomes.

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AUTHOR CONTRIBUTIONS

Hiroki Nakajima: Conceptualization, Data curation, Writing. **Junpei Yamaguchi:** Data curation. **Hideki Takami:** Data curation. **Masamichi Hayashi:** Data curation. **Yasuhiro Kodera:** Data curation. **Yoshihiro Nishida:** Data curation. **Nobuyuki Watanabe:** Data curation. **Shunsuke Onoe:** Data curation. **Takashi Mizuno:** Data curation. **Yukihiro Yokoyama:** Conceptualization, Data curation, Writing, Validation. **Tomoki Ebata:** Conceptualization, Validation.

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DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy reasons.

DECLARATIONS

Conflicts of interest: The authors have no conflicts of interest to declare

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FIGURE LEGENDS

Fig. 1

Flowchart of the participants

Fig. 2

Histogram of normalized total psoas muscle area among patients with borderline resectable pancreatic cancer.

Gray bar, patients who could undergo resection; black bar, patients who could not undergo resection due to an advanced tumor.

Fig. 3

Kaplan–Meier curves for overall survival in patients with (A) resectable pancreatic cancer and (B) borderline resectable pancreatic cancer.

Supplementary Fig. 1

Abdominal computed tomography image at the level of the third lumbar vertebra. The right and left psoas muscle areas, which comprise the total psoas muscle area (TPA), were traced (dotted line). Normalized TPA = measured TPA [mm^2]/height [$m]^2$.

Supplementary Fig. 2

Kaplan–Meier curves for recurrence free survival in patients with (A) resectable pancreatic cancer and (B) borderline resectable pancreatic cancer.

Table 1 Baseline characteristics of patients with resectable pancreatic cancer

Variables	Normal-TPA (n = 29)	Low-TPA (n = 15)	*p* Value
Baseline characteristics of the patients before neoadjuvant chemotherapy			
Age (years)	72 (63–76)	73 (71–74)	0.691
Male gender [n (%)]	18 (62)	9 (60)	0.894
Height (m)	1.62 (1.54–1.68)	1.61 (1.53–1.69)	0.941
Body weight (kg)	58.0 (48.9–65.2)	50.9 (46.7–55.5)	0.095
Body mass index (kg/m^2)	21.9 (20.2–23.5)	19.3 (18.1–20.6)	0.015
Total psoas muscle area (cm^2/m^2)			
Male	9.00 (8.26–10.41)	7.11 (6.25–7.67)	<0.001
Female	6.75 (6.30–7.05)	5.52 (5.25–5.60)	<0.001
Tumor location [n (%)]			0.464
Head	24 (83)	11 (73)	
Body, tail	5 (17)	4 (27)	
Charlson comorbidity index (0/1/>1)	10/8/11	3/5/7	0.719
Prognostic score			
Prognostic nutritional index	43 (42–45)	44 (41–46)	0.803
modified glasgow prognostic score (0/1/2)	14/11/4	7/7/1	0.824
C-reactive protein to albumin ratio	0.11 (0.01–0.37)	0.03 (0.01–0.15)	0.488
Neutrophil to lymphocyte ratio	2.36 (1.81–3.64)	2 (1.51–2.68)	0.173
Platelet-to-lymphocyte ratio	166 (114–227)	153 (124–209)	0.720
Tumor size (mm)	25.0 (21.0–30.0)	18.0 (17.5–23.5)	0.002
CA 19-9 serum level (U/mL)	145 (57–580)	54 (26–348)	0.287
Treatment details and treatment response			
Chemotherapy regimen [n (%)]			0.376
FOLFIRINOX	1 (3)	0 (0)	
Gemcitabine + nab-paclitaxel	3 (10)	0 (0)	
Gemcitabine + S-1	25 (86)	14 (93)	
S-1	0 (0)	1 (7)	
Duration of chemotherapy (days)	49 (41–55)	35 (20–41)	0.016
Relative dose intensity	1.00 (1.00–1.00)	0.96 (0.50–1.00)	0.010
Rate of chemotherapy completion [n (%)]	23 (79)	7 (47)	0.042
Change of tumor size (mm)	-5 (-8–-2)	0 (-2–0)	0.008
RECIST criteria [n (%)]			0.452
Complete response / Partial response	8 (28)	2 (13)	
Stable disease / Progressive disease	21 (72)	13 (87)	
Adverse events Grade ≥3 [n (%)]			
Any hematotoxicity	15 (52)	11 (73)	0.208
Leukopenia	5 (17)	7 (47)	0.071
Neutropenia	15 (52)	10 (67)	0.522
Platelets	0 (0)	1 (7)	0.341
Resection [n (%)]	29 (100)	15 (100)	NA

Type of operation [n (%)]			0.468
Pancreaticoduodenectomy	23 (79)	10 (67)	
Distal or total pancreatectomy	6 (21)	5 (33)	
Combined resection [n (%)]			
Portal vein	5 (17)	6 (40)	0.144
Artery	0 (0)	0 (0)	NA
Operation time (min)	402 (347–449)	368 (316–483)	0.569
Blood loss (ml)	660 (365–915)	440 (243–1179)	0.683
Evans grading [n (%)]			0.647
Grade IIb, III, IV	5 (17)	1 (7)	
Grade I, IIa	24 (83)	14 (93)	
R0 resection [n (%)]	26 (90)	14 (93)	1.000
Clavien-Dindo grade ≥3 [n (%)]	11 (28)	2 (13)	0.162
Postoperative hospital stays (days)	24 (17–33)	21 (19–23)	0.511
Adjuvant chemotherapy [n (%)]	23 (79)	13 (87)	0.695

Data are presented as median (interquartile range [IQR]) or n (%). *CA 19-9 serum level* carbohydrate antigen 19-9 serum level, *FOLFIRINOX* combination of fluorouracil, leucovorin, oxaliplatin, and irinotecan, *RECIST criteria*, Response Evaluation Criteria in Solid Tumors criteria. *NA* not applicable.

Table 2 Baseline characteristics of patients with borderline resectable pancreatic cancer

Variables	Normal-TPA (n = 48)	Low-TPA (n = 23)	*p* Value
Baseline characteristics of the patients before neoadjuvant chemotherapy			
Age (years)	68 (60–72)	66 (59–72)	1.000
Male gender [n (%)]	28 (58)	14 (61)	0.839
Height (m)	1.61 (1.55–1.66)	1.61 (1.53–1.69)	0.658
Body weight (kg)	56.7 (48.6–63.1)	52.6 (44.4–59.4)	0.078
Body mass index (kg/m^2)	22.1 (20.4–23.5)	19.7 (18.7–20.7)	0.001
Total psoas muscle area (cm^2/m^2)			
Male	8.35 (7.55–9.53)	6.20 (5.63–6.88)	<0.001
Female	7.30 (7.02–8.15)	5.36 (4.99–6.10)	<0.001
Tumor location [n (%)]			0.234
Head	14 (29)	3 (13)	
Body, tail	34 (71)	20 (87)	
Charlson comorbidity index (0/1/>1)	27/15/6	9/11/3	0.359
Prognostic score			
Prognostic nutritional index	44.5 (42–47)	43 (37–46)	0.158
modified glasgow prognostic score (0/1/2)	34/11/3	13/7/3	0.369
C-reactive protein to albumin ratio	0.06 (0.01–0.13)	0.04 (0.01–0.07)	0.535
Neutrophil to lymphocyte ratio	2.29 (1.74–3.87)	2.33 (1.49–3.2)	0.606
Platelet-to-lymphocyte ratio	167 (126–208)	172 (116–210)	0.768
Tumor size (mm)	27.5 (22.0–32.0)	30.0 (25.0–36.0)	0.108
CA 19-9 serum level (U/mL)	279 (45–943)	67 (20–456)	0.231
Treatment details and treatment response			
Chemotherapy regimen [n (%)]			<0.001
FOLFIRINOX	22 (46)	1 (4)	
Gemcitabine + nab-paclitaxel	24 (50)	22 (96)	
Gemcitabine + S-1	2 (4)	0 (0)	
S-1	0 (0)	0 (0)	
Duration of chemotherapy (days)	60 (49–77)	59 (49–128)	0.610
Relative dose intensity	1.00 (1.00–1.00)	1.00 (0.89–1.00)	0.007
Rate of chemotherapy completion [n (%)]	39 (81)	9 (39)	0.001
Change of tumor size (mm)	-4 (-7–-1)	-1 (-8–0)	0.274
RECIST criteria [n (%)]			0.359
Complete response / Partial response	8 (17)	6 (26)	
Stable disease / Progressive disease	40 (83)	17 (74)	
Adverse events Grade ≥3 [n (%)]			
Any hematotoxicity	27 (56)	16 (70)	0.313
Leukopenia	13 (27)	8 (35)	0.582
Neutropenia	27 (56)	16 (70)	0.313
Platelets	4 (8)	2 (9)	1.000
Resection [n (%)]	46 (96)	16 (70)	0.004

Type of operation [n (%)]*			0.582
Pancreaticoduodenectomy	34 (74)	13 (81)	
Distal or total pancreatectomy	12 (26)	3 (19)	
Combined resection [n (%)]*			
Portal vein	37 (80)	13 (81)	1.000
Artery	9 (20)	4 (25)	0.725
Operation time (min)*	487 (439–536)	506 (416–590)	0.797
Blood loss (ml)*	1075 (668–1532)	888 (652–1613)	0.541
Evans grading [n (%)]*			0.713
Grade IIb, III, IV	9 (20)	2 (13)	
Grade I, IIa	37 (80)	14 (88)	
R0 resection [n (%)]*	38 (79)	9 (39)	0.046
Clavien-Dindo grade ≥3 [n (%)]	5 (11)	3 (19)	0.414
Postoperative hospital stays (days)*	23 (19–28)	23 (19–24)	0.735
Adjuvant chemotherapy [n (%)]*	41 (89)	14 (88)	1.000

Data are presented as median (interquartile range [IQR]) or n (%). *CA 19-9 serum level* carbohydrate antigen 19-9 serum level, *FOLFIRINOX*, combination of fluorouracil, leucovorin, oxaliplatin, and irinotecan, *RECIST criteria*, Response Evaluation Criteria in Solid Tumors criteria. *n = 62

Table 3 Unadjusted and adjusted Cox regression analyses for overall survival and recurrence-free survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p* Value	HR	95%CI	*p* Value
Overall survival						
Resectable pancreatic cancer (n = 44)						
Indicator						
Normal-TPA	1.00	[Reference]		1.00	[Reference]	
Low-TPA	1.71	0.38–7.68	0.482	1.43	0.27–7.53	0.670
Age, per SD increase	0.92	0.44–1.91	0.823	1.26	0.54–2.94	0.586
Male	6.18	0.77–49.57	0.086	8.10	0.81–81.18	0.075
Body mass index, SD decrease	1.04	0.5–2.16	0.915	1.33	0.44–4.02	0.616
Borderline resectable pancreatic cancer (n = 71)						
Indicator						
Normal-TPA	1.00	[Reference]		1.00	[Reference]	
Low-TPA	2.98	1.33–6.70	0.008	2.57	1.06–6.24	0.037
Age, per SD increase	1.11	0.75–1.65	0.612	1.05	0.68–1.62	0.818
Male	1.49	0.66–3.39	0.336	1.92	0.82–4.47	0.133
Body mass index, SD decrease	1.53	0.99–2.35	0.055	1.38	0.86–2.22	0.182
Recurrence-free survival						
Resectable pancreatic cancer (n = 44)						
Indicator						
Normal-TPA	1.00	[Reference]		1.00	[Reference]	
Low-TPA	0.38	0.13–1.11	0.075	0.37	0.12–1.13	0.080
Age, per SD increase	1.33	0.87–2.03	0.185	1.32	0.86–2.02	0.203
Male	0.98	0.43–2.22	0.965	1.20	0.49–2.91	0.694
Body mass index, SD decrease	0.91	0.60–1.39	0.672	1.09	0.67–1.77	0.740
Borderline resectable pancreatic cancer (n = 62)						
Indicator						
Normal-TPA	1.00	[Reference]		1.00	[Reference]	
Low-TPA	1.60	0.84–3.06	0.151	1.65	0.8–3.38	0.173
Age, per SD increase	1.19	0.88–1.60	0.268	1.19	0.85–1.65	0.310
Male	0.88	0.49–1.57	0.667	0.99	0.54–1.80	0.961
Body mass index, SD decrease	1.06	0.80–1.40	0.705	0.94	0.69–1.28	0.700

TPA total psoas area**,** *CI* confidence interval, *HR* hazard ratio, *SD* standard deviation.

Survival analysis was performed using a univariate Cox proportional hazards model. Variables of baseline characteristics of the patients before neoadjuvant chemotherapy (TPA, age, sex, and body mass index) were incorporated into multivariate analysis.

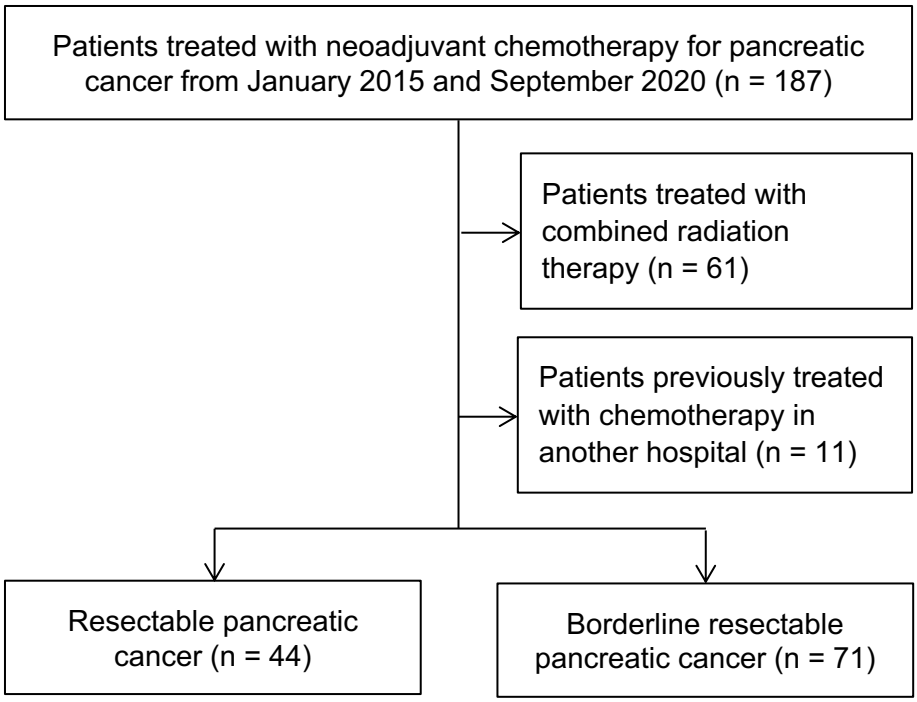

Patients treated with neoadjuvant chemotherapy for pancreatic cancer from January 2015 and September 2020 (n = 187)
Patients treated with combined radiation therapy (n = 61)
Patients previously treated with chemotherapy in another hospital (n = 11)
Resectable pancreatic cancer (n = 44)
Borderline resectable pancreatic cancer (n = 71)

Fig. 1

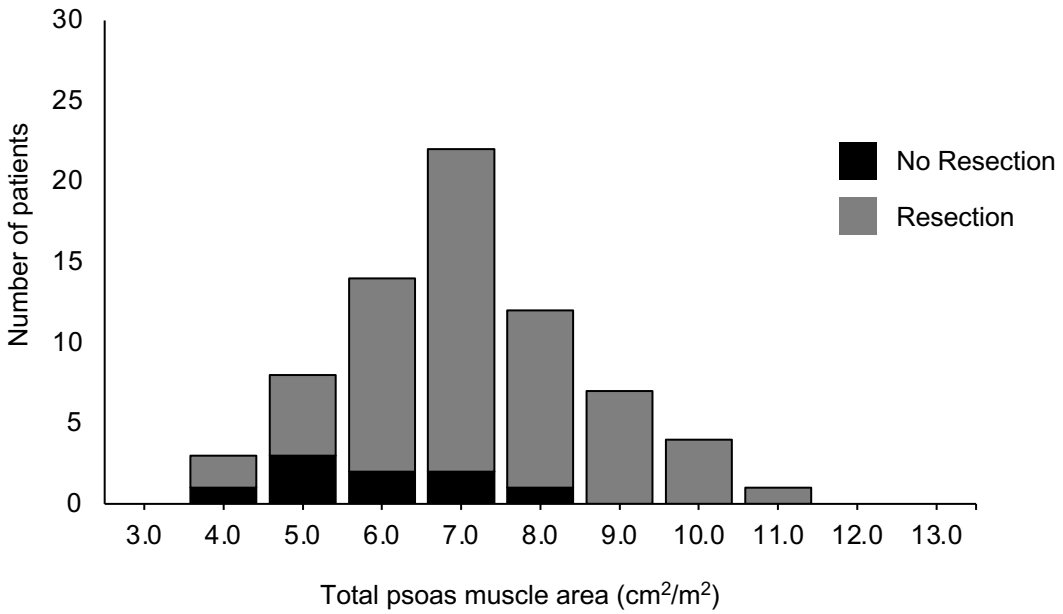
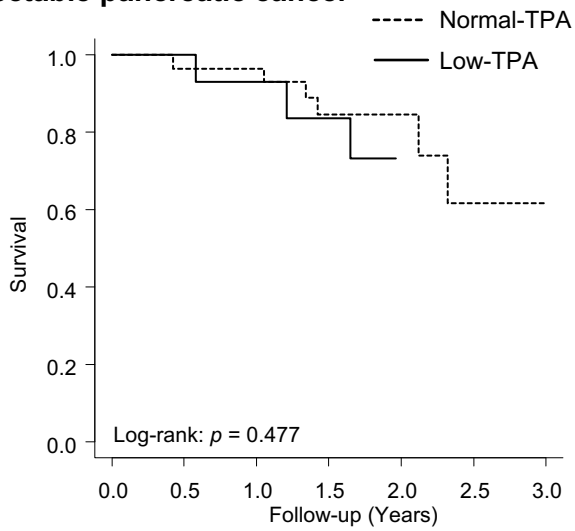

30
25
20
15
10
5
0
Number of patients
No Resection
Resection
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
Total psoas muscle area (cm2/m2)

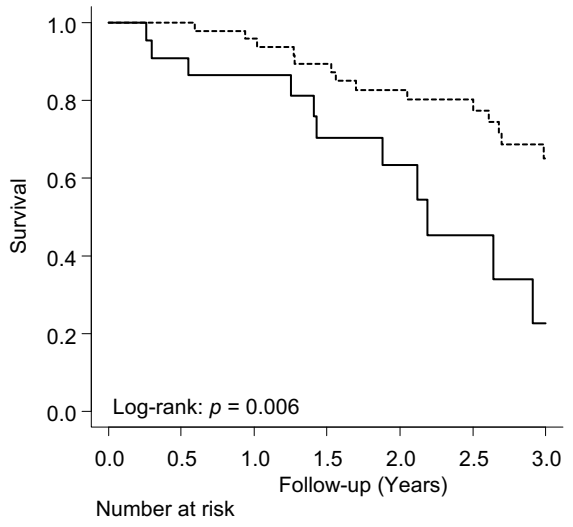
Fig. 2

A. Resectable pancreatic cancer



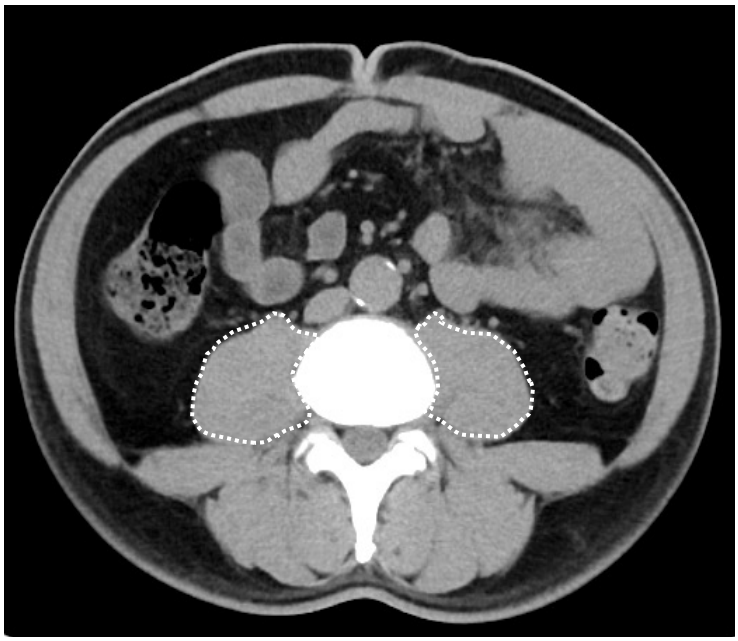
Number at risk							
Normal-TPA	29	27	27	19	10	2	1
Low-TPA	15	15	10	9	0	0	0

B. Borderline resectable pancreatic cancer



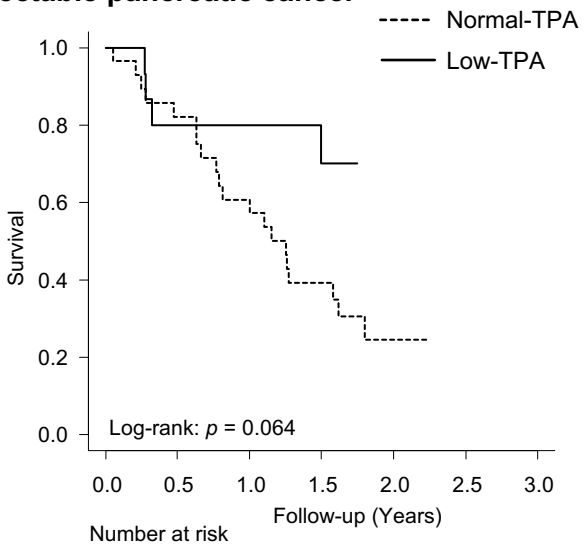
Number at risk							
Normal-TPA	48	47	45	41	34	28	18
Low-TPA	23	20	17	13	9	4	2

Fig. 3



Supplementary Fig. 1

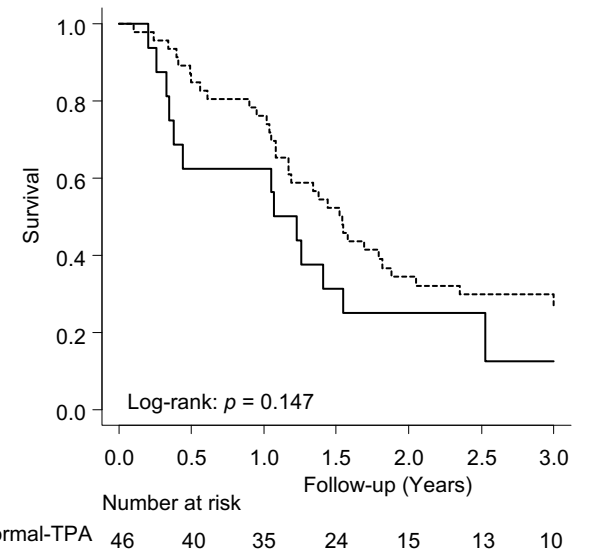
A. Resectable pancreatic cancer



Number at risk

Normal-TPA	29	23	17	9	2	0	0
Low-TPA	15	10	9	8	0	0	0

B. Borderline resectable pancreatic cancer



Number at risk

Normal-TPA	46	40	35	24	15	13	10
Low-TPA	16	10	10	5	2	2	1

Supplementary Fig. 2