# Clinical impact of body composition on postoperative outcomes during neoadjuvant chemoradiation therapy for distal bile duct cancer

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**Abstract.** Body composition changes during neoadjuvant therapy and their clinical significance have not been clarified. The present study aimed to investigate body composition changes during neoadjuvant chemoradiation therapy (NACRT) in patients with distal bile duct cancer and the clinical impact on postoperative complications and the prognosis. A total of 16 patients with distal bile duct cancer who underwent curative resection after NACRT were retrospectively evaluated. The area of skeletal muscle, visceral fat and subcutaneous fat on computed tomography and immunological and nutritional indices were assessed before and after NACRT. All 16 patients completed NACRT followed by pancreaticoduodenectomy without mortality. There was no significant change in the skeletal muscle mass index (SMI) during NACRT. Of the 16 patients, nine (56%) were defined as sarcopenic before NACRT, and eight (50%) met the criteria for sarcopenic after NACRT. The SMI and total fat area were significantly associated with postoperative pancreatic fistula (POPF) (P=0.019 and P=0.007, respectively). The patients with sarcopenia had a shorter disease-free survival time and overall survival time in comparison to patients without sarcopenia (P=0.025 and P=0.115, respectively). In conclusion, NACRT for distal bile duct cancer did not significantly affect the body composition, or the immunological or nutritional indices. Sarcopenia after NACRT was significantly associated with early recurrence in patients with distal bile duct cancer who received NACRT.

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*Abbreviations:* NACRT, neoadjuvant chemoradiation therapy; SMI, skeletal muscle index; POPF, postoperative pancreatic fistula; OS, overall survival; DFS, disease-free survival; NAC, neoadjuvant chemotherapy; BMI, body mass index; PTCD, percutaneous transhepatic cholangiodrainage; ERBD, endoscopic retrograde biliary drainage; BUN, blood urea nitrogen; CRP, C reactive protein; PNI, prognostic nutrition index; NLR, neutrophil-to-lymphocyte ratio; ISGPF, International Study Group on Pancreatic Fistula

*Key words:* bile duct cancer, neoadjuvant therapy, sarcopenia, skeletal muscle mass index

## Introduction

Distal bile duct cancer is rare and surgical resection is the only treatment that offers the opportunity for a cure. However, the 5-year survival rate after surgical resection is as low as 40% (1). To improve the surgical outcomes, appropriate neoadjuvant therapy or adjuvant chemotherapy would be desired as an alternative approach. Neoadjuvant chemotherapy (NAC) or neoadjuvant chemo-radiation therapy (NACRT) has been widely adopted for the treatment of various solid cancers and has been reported to improve the prognosis after surgery. We previously reported that surgery following NACRT was associated with a good prognosis in patients with pancreatic cancer or bile duct cancer (2,3).

Several body composition parameters, for example the body mass index (BMI), skeletal muscle mass, and total fat mass have been reported to be associated with postoperative morbidity or the prognosis of various types of cancer. Some reports showed that the body composition changed during neoadjuvant treatment and that the body composition parameters of were associated with postoperative complications. However, the change in body composition during NACRT for patients with distal bile duct cancer and its influence on the prognosis has not been clarified.

The aim of this study was to investigate the impact of NACRT on the body composition of patients with distal bile duct cancer, and to evaluate the influence of body composition and its changes on postoperative complications and the prognosis.

## Patients and methods

*Patients and data collection*. This study retrospectively analyzed 16 patients with distal bile duct cancer who

underwent chemoradiation therapy followed by surgery between March 2006 and December 2015 in our institute. The clinicopathological characteristics of these patients are shown in Table I. All patients needed preoperative biliary drainage due to obstructive jaundice. Four patients underwent percutaneous transhepatic cholangiodrainage and twelve underwent endoscopic retrograde biliary drainage. They were diagnosed with resectable distal extrahepatic bile duct cancer, and received gemcitabine-based neoadjuvant chemoradiation therapy after histological or cytological confirmation of bile duct cancer. After the completion of NACRT, pancreaticoduodenectomy with extensive regional lymphadenectomy was performed. We collected the following data at the diagnosis and after NACRT of white blood cell count, neutrophil count, lymphocyte count, hemoglobin, platelet count, and the serum levels of total protein, albumin, blood urea nitrogen (BUN), creatinine and C reactive protein (CRP). The prognostic nutrition index (PNI) and the neutrophil-to-lymphocyte ratio (NLR) were calculated according to these results. The PNI was calculated using the following equation: PNI = 10 x serum albumin (mg/dl) + 0.005 x total lymphocyte count. In the present study, the cutoff values for the PNI and NLR were 40 and 2.5, respectively.

*Definition of adverse events during chemo-radiation therapy and surgical complication*. We retrospectively collected information related to adverse events during NACRT and the complications after surgery. Adverse events during NACRT were graded according to the Common Terminology Criteria for Adverse Events version 4.0, and postoperative complications were defined as any complication classified as grade 2 (requiring pharmacological treatment) or higher, according to the Clavien-Dindo classification (4).

Table I. Clinical characteristics of 16 patients who received preoperative chemoradiation.

| Patient characteristics (n=16) | Values |
|---|---|
| Age, median years (range) | 64.5 (40-76) |
| Gender (male:female) | 11:5 |
| Tumor depth (T1:T2:T3:T4) | 1:5:10:0 |
| Nodal status (N0:N1) | 14:2 |
| Stage (IA:IB:IIA:IIB) | 1:5:8:2 |
| Tumor differentiation (well:moderately:poorly) | 7:5:4 |
| Residual tumor (R0:R1) | 16:0 |
| CA19-9, median (range) (U/ml) | 15 (2-154) |
| CEA, median (range) (mg/dl) | 2.65 (1.3-6) |
| Cycle of chemo Tx (2:3) | 6:10 |
| Dosages of RT (50 Gy:60 Gy) | 12:4 |
| Period of CRT to operation (day) | 100 (70-121) |
| Chemotherapy-induced toxicity (≥ grade 3) | |
| Hematological | 9 |
| Non-hematological | 2 |
| Postoperative complication | |
| Clavien-Dindo grade ≥2 | 10 |
| POPF (ISGPF grade ≥B) | 6 |

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRT, chemoradiation therapy; POPF, postoperative pancreatic fistula.

*Preoperative gemcitabine-based chemoradiation therapy and adjuvant chemotherapy*. The protocol of gemcitabine-based chemoradiation therapy has reported previously (1). In brief, the intravenous administration of gemcitabine (1,000 mg/m$^2$) was concurrently initiated on days 1, 8, and 15 during each four-week cycle, and repeated for two or three cycles. 3 dimensional radiation was administered at a total dosage of 50-60 Gy with a daily fraction of 2-2.4 Gy 5 times per week, which targeted the primary distal bile tumor with the surrounding lymph nodes it, the para-aortic region, and the retroperitoneal soft tissue. All protocols were conducted after obtaining written informed consent from all patients in accordance with the approved procedure at our hospital. Patients eligible for enrollment were confirmed before the initiation of NACRT. The criteria for the patients were as follows: resectable distal bile duct cancer, subserosal or deeper tumor invasion, and no evidence of distant metastases. The introduction of adjuvant chemotherapy and the regimens of anticancer drugs were decided based on the evaluation of the attending physicians and the patient's performance status. Among the 16 patients, 6 (37%) received gemcitabine, and 3(19%) received TS-1 after surgery. The adjuvant S-1 group received 4 cycles of oral TS-1 chemotherapy at the dose of 40 mg/m$^2$ twice daily for 4 weeks, followed by 2 weeks of rest.

*Evaluation of skeletal muscle, visceral fat, and subcutaneous fat by computed tomography*. The skeletal muscle area, visceral fat area and subcutaneous fat area were assessed by computed tomography before and after NACRT using the Zio station 2 (Ziosoft, Inc.) software program (Fig. 1). The skeletal muscle area was measured as the cross-sectional area of the total skeletal muscle area at the level of middle portion of the 3rd lumbar vertebra by manual tracing. The visceral fat and subcutaneous fat area were also measured at the level of middle portion of the 3rd lumbar vertebra by applying a threshold with an attenuation range of -60 to -120 Hounsfield units. The skeletal muscle index (SMI) was calculated with the following equation: (cm$^2$/m$^2$) = skeletal muscle area (cm$^2$)/height (m$^2$). Sarcopenia was defined as an SMI of 42 cm$^2$/m$^2$ in males and 38 cm$^2$/m$^2$ in females according to Japan Society of Hepatology guidelines for sarcopenia in liver disease (1st edition) (5).

*Statistical analysis*. The data were analyzed using JMP® 13 (SAS Institute Inc.). Categorical variables were reported as numbers and percentages, while continuous variables were reported as the median and range. The Fisher's exact test was used for the comparison of categorical variables, and the Mann-Whitney U test was used for the comparison of continuous variables. The Wilcoxon signed-rank test was used for the comparison between paired samples. Pearson's correlation analysis was performed to analyze the correlation between SMI and total fat area. Survival rates were calculated using the Kaplan-Meier methods and compared using a log-rank

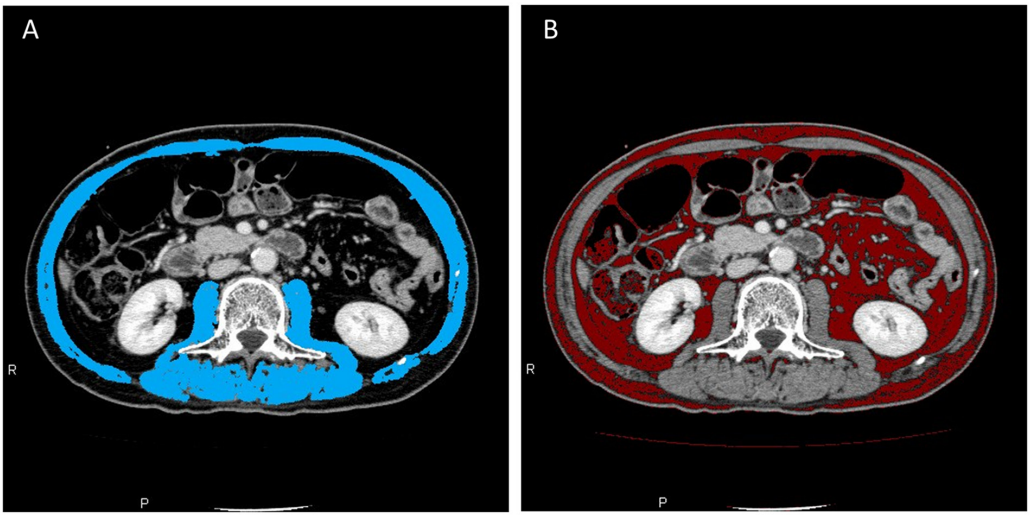


Figure 1. Cross-sectional computed tomographic images of the middle portion of the 3rd lumbar vertebra level. (A) Skeletal muscle area was measured using manual tracing. (B) After applying threshold with an attenuation range of -60 to -120 Hounsfield units to generate a fat-density mask, the fat area was measured in the region of interest.

test. P-values of <0.05 were considered to indicate statistical significance.

## Results

*The clinical course and short-term outcomes*. All 16 patients completed NACRT followed by pancreaticoduodenectomy without mortality. The median period from NACRT to operation was 100 days (range, 70-121). Six patients (37%) experienced grade ≥3 adverse events. Grade ≥2 complications were observed in 10 patients (62%). The most common complication was postoperative pancreatic fistula (POPF) which occurred in six patients (37%) (Table I).

*Change in laboratory test parameters, immunological and nutritional indices, and the body composition*. The results of laboratory tests, immunological and nutritional indices, and the body composition of before and after NACRT are shown in Table II. There was no significant change in the neutrophil count, platelet count, total protein, albumin, BUN, creatinine, CRP from before to after NACRT. The lymphocyte count (P=0.0076) and hemoglobin level (P=0.001) significantly decreased after NACRT. The median PNI and NLR were 42.7 (range, 30.8-50.3) and 1.89 (range, 1.06-5.07) before NACRT, and 40.8 (range, 32.4-50.1) and 2.46 (range, 1.0-5.12) after NACRT. There was no significant difference in the pre-NACRT and post-NACRT values.

The median SMI in males was 44.6 $cm^2/m^2$ (range, 26.2-57.6) before NACRT and 44.4 $cm^2/m^2$ (range, 29.6-51.2) after NACRT. The median SMI in females was 30.5 $cm^2/m^2$ (range, 27.2-33.6) before NACRT, and 31.5 $cm^2/m^2$ (range, 28.5-39.0) after NACRT. The total SMI before and after NACRT did not differ to a statistically significant extent (Fig. 2A). In male patients, there was a significant correlation between total fat area and SMI after NACRT (R=0.602 and P=0.049). Nine (56%) of the 16 patients were identified as sarcopenic before NACRT. Eight (50%) patients met the criteria for sarcopenia after NACRT. Among all nine patients with sarcopenia before NACRT, only one who had sarcopenia before NACRT recovered after NACRT, whereas the other eight patients remained sarcopenic after NACRT. Only two patients required a reduction in the dosage of NACRT, including one with sarcopenia. After NACRT, the median BMI, subcutaneous fat area and total fat area at the level of the middle portion of the 3rd lumbar vertebra were smaller in comparison to before NACRT; however, the differences were not statistically significant (Fig. 2B).

*Association of the body composition and immunological and nutritional indices with postoperative complications*. POPF, intra-abdominal abscess, chylous ascites, diarrhea, and delayed gastric empty were observed in this study. We also focused on POPF because it is one of the most important and frequent complications after pancreaticoduodenectomy. The patients with POPF (ISGPF B or C) had a significantly greater SMI and total fat area than patients without POPF (P=0.019, and P=0.007, respectively). There was no significant association between the incidence of postoperative complications and the NLR, PNI, or sarcopenia after NACRT (Tables III and IV).

*Association of the body composition and immunological and nutritional indices with the long-term outcomes*. Patients with sarcopenia had significantly shorter disease-free survival in comparison to those without sarcopenia (P=0.025). The 3-year overall survival rate of patients without sarcopenia was 100%, while that of patients with sarcopenia was 71%; however, the difference was not statistically significant (Fig. 3). The SMI, total fat area, PNI, and NLR were not correlated with the overall and disease-free survival rates. Adjuvant chemotherapy was introduced in 9 (56%) of 16 patients, and only 2 needed to have the dosage of adjuvant chemotherapy reduced, while 1 required cessation of therapy. There was no significant difference between receiving a reduced dose of adjuvant chemotherapy and the presence of sarcopenia (Table V). The induction rate

Table II. Clinical characteristics of patients before (pre-NACRT) and after (post-NACRT) neoadjuvant chemoradiation therapy.

| Patient Characteristics | Pre-NACRT | Post-NACRT | P-value |
|---|---|---|---|
| Weight (kg) | 57.9 (78.0-44.6) | 58.7 (76.7-43.3) | 0.368 |
| SMI ($cm^2/m^2$) | 37.2 (57.6-26.2) | 38.9 (51.2-28.5) | 0.899 |
| Total fat area ($cm^2$) | 168.8 (25.9-296.6) | 130.9 (14.6-276.4) | 0.211 |
| Subcutaneous fat area ($cm^2$) | 72.8 (19.2-140.8) | 67.1 (8.3-152.9) | 0.159 |
| Visceral fat area ($cm^2$) | 63.5 (6.6-195.1) | 67.4 (4.2-143.6) | 0.211 |
| Neutrophil count ($10^3/\mu l$) | 2067 (1216-5176) | 1860 (1018-3880) | 0.322 |
| Lymphocyte count ($10^3/\mu l$) | 1363 (762-2302) | 772 (458-2025) | 0.007 |
| Hemoglobin (g/dl) | 12.0 (10.3-14.3) | 11.0 (9.4-12.1) | 0.001 |
| Platelet count ($10^3/\mu l$) | 239 (171-411) | 256 (107-597) | 0.355 |
| Albumin (g/dl) | 3.4 (2.5-4.0) | 3.6 (2.8-4.4) | 0.392 |
| CRP (mg/dl) | 0.18 (0.01-2.66) | 0.30 (0.04-5.49) | 0.426 |
| PNI | 42.7 (30.8-50.3) | 40.8 (32.4-50.1) | 0.705 |
| NLR | 1.89 (1.06-5.07) | 2.46 (1.00-5.12) | 0.322 |

The data are presented as median (range). NACRT, neoadjuvant chemoradiation therapy; PNI, prognostic nutrition index; SMI, skeletal muscle index; CRP, C reactive protein; NLR, neutrophil-to-lymphocyte ratio.

Table III. Relationship between complications and inflammation-based prognostic scores or body composition.

| Post-NACRT | Complication | No complication | P-value |
|---|---|---|---|
| PNI (<40:≥40) | 4:6 | 2:4 | 0.789 |
| NLR (<2.5:≥2.5) | 6:4 | 3:3 | 0.696 |
| Sarcopenia (yes: no) | 3:7 | 5:1 | 0.118 |
| SMI ($cm^2/m^2$) | 44.9 (29.6-51.2) | 34.8 (28.5-44.4) | 0.115 |
| Total fat area ($cm^2$) | 163.4 (14.6-276.4) | 130.9 (20.8-221.1) | 0.704 |

NACRT, neoadjuvant chemoradiation therapy; POPF, postoperative pancreatic fistula; PNI, prognostic nutrition index; NLR, neutrophil-to-lymphocyte ratio; SMI, skeletal muscle index.

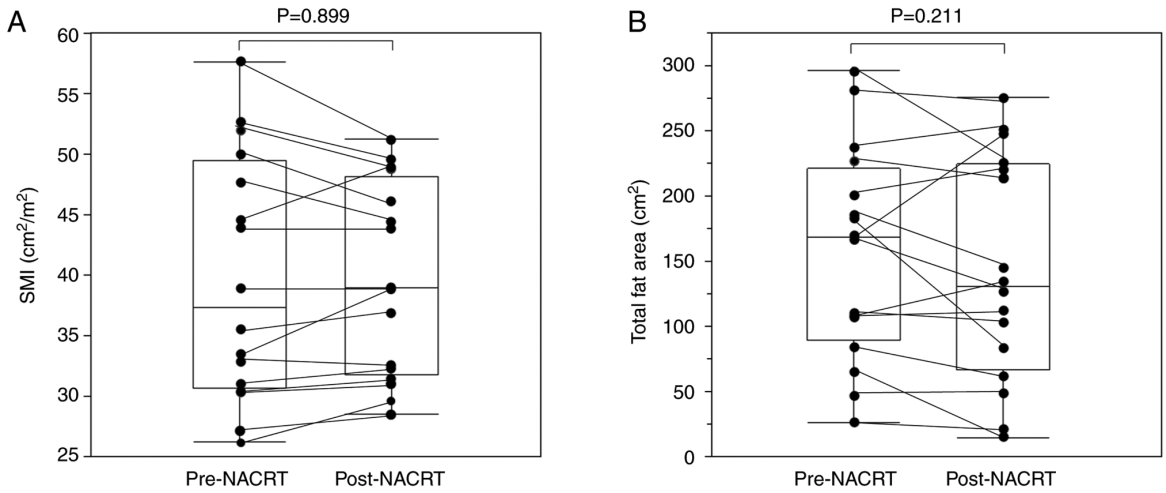


Figure 2. Change in body composition during NACRT. (A) Median SMI did not change to a statistically significant extent. (B) Median total fat area did not change to a statistically significant extent. NACRT, neoadjuvant chemoradiation therapy; SMI, skeletal muscle mass index.

of adjuvant chemotherapy was not significantly different between the patients with and without sarcopenia and was also not associated with the disease-free survival (DFS) or overall survival (OS).

Table IV. Relationship between POPF and the inflammation-based prognostic scores or body composition.

| Post-NACRT | POPF | Non-POPF | P-value |
|---|---|---|---|
| PNI (<40:≥40) | 2:4 | 4:6 | 1 |
| NLR (<2.5:≥2.5) | 3:3 | 6:4 | 1 |
| Sarcopenia (yes: no) | 1:5 | 7:3 | 0.118 |
| SMI ($cm^2/m^2$) | 48.8 (32.3-51.2) | 34.8 (28.5-45.8) | 0.019 |
| Total fat area ($cm^2$) | 237.5 (112.6-276.4) | 93.0 (14.6-213.5) | 0.007 |

NACRT, neoadjuvant chemoradiation therapy; POPF, postoperative pancreatic fistula; PNI, prognostic nutrition index; NLR, neutrophil-to-lymphocyte ratio; SMI, skeletal muscle index.

Table V. Relationship between sarcopenia and dose intensity in NACRT and adjuvant chemotherapy.

| Type of chemotherapy | Sarcopenia | Non-sarcopenia | P-value |
|---|---|---|---|
| NACRT | | | |
| Dose intensity 100:80% | 7:1 | 7:1 | >0.999 |
| Adjuvant chemotherapy | | | |
| Dose intensity 100:80% | 4:1 | 3:1 | >0.999 |
| Induction rate | 62.5% | 50% | >0.999 |

NACRT, neoadjuvant chemoradiation therapy.

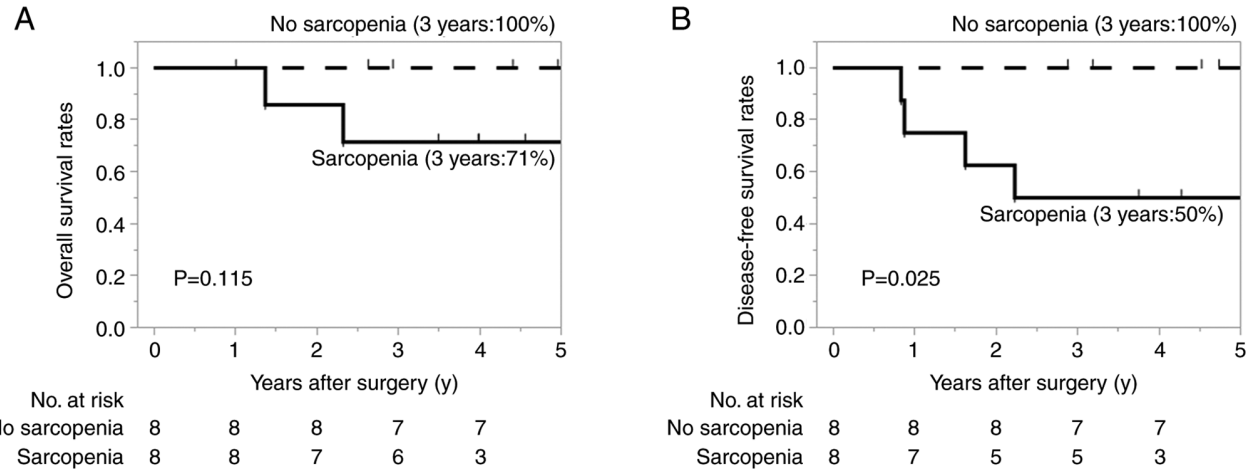


Figure 3. Overall survival and disease-free survival curves, as estimated by Kaplan-Meier methods according to the presence or absence of sarcopenia. (A) Overall survival rate in patients with sarcopenia was lower compared with that in patients without sarcopenia; however, the difference was not statistically significant. (B) Disease-free survival rate in patients with sarcopenia was significantly shorter compared with that in patients without sarcopenia (P=0.025).

## Discussion

In this study, we assessed the changes in body composition during NACRT for distal bile duct cancer, and investigated its influence on postoperative complications, disease-free and, overall survival rates. Extrahepatic bile duct cancer was divided into two major categories; proximal and distal. The surgical procedure for proximal bile duct cancer is major liver resection. On the other hand, pancreaticoduodenectomy is applied for distal bile duct cancer. The profiles of postoperative complication between major liver resection and pancreaticoduodenectomy are quite different. Therefore, we selected patients with distal bile duct for limiting the surgical procedure to pancreaticoduodenectomy only.

Our study showed that body weight, the SMI, and the total fat area were not significantly changed after NACRT. The proportion of sarcopenic patients was also unchanged after NACRT, and only one patient recovered from sarcopenia after NACRT. No significant changes in the immunological or nutri-

tional indices were observed although the lymphocyte counts and serum hemoglobin level were decreased after NACRT. Some reports showed that the SMI was significantly decreased during NACRT or NAC, others did not. The proportion of sarcopenic patients significantly increased after NAC in patients with esophageal cancer (6,7). Reisinger *et al* demonstrated that the SMI reduction during NACRT was larger in patients with stage III-IV than in those with stage I-II, and was a predictor of postoperative mortality (8). In gastric cancer, the proportion of patients with sarcopenia was also increased after NAC (9). On the other hand, the mean SMI remained unchanged after NACRT in colorectal cancer (10). These previous studies would indicate that patients with upper gastrointestinal tract cancer probably became sarcopenic during NAC because of changes of in their dietary habitat due to obstruction or stenosis by the tumor. Another possibility is that severe anorexia and nausea were only seen in 2.5-7.5 and 3.5-5%, of patients who received gemcitabine monotherapy (11,12). The change in body composition and incidence of sarcopenia during NAC or NACRT may depend on the type of cancer and the chemotherapeutic regimen. Gemcitabine monotherapy and gemcitabine plus radiation therapy for patients with distal bile duct cancer did not induce severe anorexia or nausea, and then their body compositions were not significantly changed.

In this study, body compression, sarcopenia, and immunological and nutritional index values were not associated with the total incidence of postoperative complications, although the presence of sarcopenia or lower SMI values has been associated with postoperative complications in various types of cancer including biliary tract cancer (9,13,14). Our study also found that a greater SMI and total fat area before surgery were associated with the occurrence of POPF. POPF is one of the most frequent postoperative complications after pancreaticoduodenectomy. This finding was consistent with previous studies. Mathur *et al* reported that patients with a pancreatic fistula after pancreaticoduodenectomy had significantly more intralobular and interlobular fat in the pancreas (15). Sandini *et al* also reported that the total fat volume and visceral fat volume were significantly correlated with POPF (16). In our study, the SMI was significantly associated with the total fat area in males; thus, in addition to the total fat area, the SMI was associated with POPF.

Another finding of our study is that the disease-free survival rates were significantly correlated with sarcopenia after NACRT. Sarcopenia after NACRT has been reported to be independently associated with a poor prognosis in various cancers (8,17-20). Chakedis *et al* carried out a study that included 117 patients with biliary tract cancers to assess the impact of sarcopenia after NACRT, and reported that 41 (35%) patients had sarcopenia, and that sarcopenia was associated with an increased risk of death among patients who underwent resection (17). Eriksson *et al* reported that the association between NAC and the SMI reduction in patients with resectable colorectal liver metastasis, and concluded that the patients a ≥5% SMI reduction during NAC were less likely to undergo adjuvant chemotherapy, and showed a shorter overall survival time (21). Cooper *et al* carried out a study to determine the relationship between sarcopenia after NAC or NACRT in patients with resectable pancreatic cancer and their survival rates. They reported that the degree of skeletal muscle loss was correlated with disease-free survival. They reported that pre-existing sarcopenia was associated with the dose-limiting toxicity of NAC and adjuvant chemotherapy and can have a negative impact on treatment efficacy and the prognosis (18). Another possible explanation for the negative impact of sarcopenia on long-term outcomes is that some chemokines that are secreted from muscle cells, called myokines, may prevent cancer cell growth, invasion and metastasis (22). In this study, there was a significant correlation with sarcopenia only in the DFS, not the OS. Our previous report showed that the three-year overall survival rate of the patients who received the preoperative chemo-radiation therapy was 81% (2). On the other hand, the five-year survival rate after surgical resection was 33.1% from the Japanese Biliary Tract Cancer Statistics Registry (1). We suspect that this was because of the small number of cases and the high OS rate after NACRT and surgery.

The present study was associated with some limitations. Firstly, this was a nonrandomized and retrospective study, that included a small number of patients from a single institution. Secondly, the definitions of sarcopenia were those included in the Japan Society of Hepatology Guidelines for Sarcopenia in Liver Disease (1st edition) as no uniformly agreed upon definition of sarcopenia exists.

In conclusion, gemcitabine plus radiotherapy for initially resectable distal bile duct cancer was safe, and did not significantly affect to the body composition, or immunological or nutritional indices during NACRT. We clarified that pretreatment sarcopenia after NACRT was significantly associated with early recurrence after pancreaticoduodenectomy. We should attempt to maintain an appropriate SMI during NACRT. Further accumulation of cases is necessary to reveal the impact of sarcopenia after preoperative therapy on overall survival in biliary tract cancer.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

WF, HW, HM, MO, MS and HT conceived and designed the study. WF, SH, YM, KA, HA, TS, MYamamoto, TT, NS, HH and TK acquired the data. WF, HW, NH, JN, MYasui, CM, TO and HT performed statistical analysis and interpreted the data. WF, HW, and HT drafted the manuscript. WF and HW confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

This study was approved by the ethics committee of Osaka International Cancer Institute (reference no. 1503315263).

## Patient consent for publication

The patient, or parent/guardian/next of kin provided written informed consent for the publication of any data and/or accompanying images.

## Competing interests

The authors declare that they have no competing interests.

## References


1. Miyakawa S, Ishihara S, Horiguchi A, Takada T, Miyazaki M and Nagakawa T: Biliary tract cancer treatment: 5,584 Results from the biliary tract cancer statistics registry from 1998 to 2004 in Japan. J Hepatobiliary Pancreat Surg 16: 1-7, 2009.
2. Kobayashi S, Gotoh K, Takahashi H, Akita H, Marubashi S, Yamada T, Teshima T, Nishiyama K, Yano M, Ohigashi H, *et al*: Clinicopathological features of surgically-resected biliary tract cancer following chemo-radiation therapy. Anticancer Res 36: 335-342, 2016.
3. Ohigashi H, Ishikawa O, Eguchi H, Takahashi H, Gotoh K, Yamada T, Yano M, Nakaizumi A, Uehara H, Tomita Y and Nishiyama K: Feasibility and efficacy of combination therapy with preoperative full-dose gemcitabine, concurrent three-dimensional conformal radiation, surgery, and postoperative liver perfusion chemotherapy for T3-pancreatic cancer. Ann Surg 250: 88-95, 2009.
4. Dindo D, Demartines N and Clavien PA: Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240: 205-213, 2004.
5. Nishikawa H, Shiraki M, Hiramatsu A, Moriya K, Hino K and Nishiguchi S: Japan society of hepatology guidelines for sarcopenia in liver disease (1st edition): Recommendation from the working group for creation of sarcopenia assessment criteria. Hepatol Res 46: 951-963, 2016.
6. Yip C, Goh V, Davies A, Gossage J, Mitchell-Hay R, Hynes O, Maisey N, Ross P, Gaya A, Landau DB, *et al*: Assessment of sarcopenia and changes in body composition after neoadjuvant chemotherapy and associations with clinical outcomes in oesophageal cancer. Eur Radiol 24: 998-1005, 2014.
7. Awad S, Tan BH, Cui H, Bhalla A, Fearon KC, Parsons SL, Catton JA and Lobo DN: Marked changes in body composition following neoadjuvant chemotherapy for oesophagogastric cancer. Clin Nutr 31: 74-77, 2012.
8. Reisinger KW, Bosmans JW, Uittenbogaart M, Alsoumali A, Poeze M, Sosef MN and Derikx JP: Loss of skeletal muscle mass during neoadjuvant chemoradiotherapy predicts postoperative mortality in esophageal cancer surgery. Ann Surg Oncol 22: 4445-4452, 2015.
9. Mirkin KA, Luke FE, Gangi A, Pimiento JM, Jeong D, Hollenbeak CS and Wong J: Sarcopenia related to neoadjuvant chemotherapy and perioperative outcomes in resected gastric cancer: A multi-institutional analysis. J Gastrointest Oncol 8: 589-595, 2017.
10. Levolger S, Van Vledder MG, Alberda WJ, Verhoef C, De Bruin RWF, Ijzermans JNM and Burger JW: Muscle wasting and survival following pre-operative chemoradiotherapy for locally advanced rectal carcinoma. Clin Nutr 37: 1728-1735, 2018.
11. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, *et al*: Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 362: 1273-1281, 2010.
12. Okusaka T, Ishii H, Funakoshi A, Yamao K, Ohkawa S, Saito S, Saito H and Tsuyuguchi T: Phase II study of single-agent gemcitabine in patients with advanced biliary tract cancer. Cancer Chemother Pharmacol 57: 647-653, 2006.
13. Otsuji H, Yokoyama Y, Ebata T, Igami T, Sugawara G, Mizuno T and Nagino M: Preoperative sarcopenia negatively impacts postoperative outcomes following major hepatectomy with extrahepatic bile duct resection. World J Surg 39: 1494-1500, 2015.
14. Pamoukdjian F, Bouillet T, Levy V, Soussan M, Zelek L and Paillaud E: Prevalence and predictive value of pre-therapeutic sarcopenia in cancer patients: A systematic review. Clin Nutr 37: 1101-1113, 2018.
15. Mathur A, Pitt HA, Marine M, Saxena R, Schmidt CM, Howard TJ, Nakeeb A, Zyromski NJ and Lillemoe KD: Fatty pancreas: A factor in postoperative pancreatic fistula. Ann Surg 246: 1058-1064, 2007.
16. Sandini M, Bernasconi DP, Ippolito D, Nespoli L, Baini M, Barbaro S, Fior D and Gianotti L: Preoperative computed tomography to predict and stratify the risk of severe pancreatic fistula after pancreatoduodenectomy. Medicine (Baltimore) 94: e1152, 2015.
17. Chakedis J, Spolverato G, Beal EW, Woelfel I, Bagante F, Merath K, Sun SH, Chafitz A, Galo J, Dillhoff M, *et al*: Pre-operative sarcopenia identifies patients at risk for poor survival after resection of biliary tract cancers. J Gastrointest Surg 22: 1697-1708, 2018.
18. Cooper AB, Slack R, Fogelman D, Holmes HM, Petzel M, Parker N, Balachandran A, Garg N, Ngo-Huang A, Varadhachary G, *et al*: Characterization of anthropometric changes that occur during neoadjuvant therapy for potentially resectable pancreatic cancer. Ann Surg Oncol 22: 2416-2423, 2015.
19. Shachar SS, Williams GR, Muss HB and Nishijima TF: Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. Eur J Cancer 57: 58-67, 2016.
20. Okumura S, Kaido T, Hamaguchi Y, Fujimoto Y, Kobayashi A, Iida T, Yagi S, Taura K, Hatano E and Uemoto S: Impact of the preoperative quantity and quality of skeletal muscle on outcomes after resection of extrahepatic biliary malignancies. Surgery 159: 821-833, 2016.
21. Eriksson S, Nilsson JH, Strandberg Holka P, Eberhard J, Keussen I and Sturesson C: The impact of neoadjuvant chemotherapy on skeletal muscle depletion and preoperative sarcopenia in patients with resectable colorectal liver metastases. HPB (Oxford) 19: 331-337, 2017.
22. Pratesi A, Tarantini F and Di Bari M: Skeletal muscle: An endocrine organ. Clin Cases Miner Bone Metab 10: 11-14, 2013.