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Original article

Predictive value of pancreatic dose-volume metrics on sarcopenia rate in gastric cancer patients treated with adjuvant chemoradiotherapy

Yi Li, Wen-bo Wang, Huan-gang Jiang, Jing Dai, Ling Xia, Ji Chen, Cong-hua Xie, Jin Peng, Zheng-kai Liao, Yan Gao, Yun-feng Zhou, Fu-xiang Zhou*

Zhongnan Hospital of Wuhan University, Department of Oncology, Wuhan University, Wuhan, 430071, China

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SUMMARY

Objective: To evaluate the relationship of sarcopenia with the pancreatic dose-volume histogram (DVH) in gastric cancer patients treated with adjuvant chemoradiotherapy (CRT) after radical gastrectomy.

Methods: A retrospective study was performed on the data in Zhongnan Hospital of Wuhan University from January 2008 to December 2016. Skeletal muscle index (SMI) was analyzed by cross-sectional areas of body composition at the level of third lumbar (L3) vertebrae, which was measured using single-slice computer tomograph (CT) prior to CRT, at 6 months and 12 months after CRT respectively. Logistic regression analysis was conducted to explore the potential clinical risk factors of sarcopenia in this patients cohort. Regarding the dosimetrics of pancreas, the sarcopenia rate was compared between the two groups divided according to the cut-off value determined by the receiver operating characteristic (ROC) curves.

Results: One hundred and fifty-three gastric cancer patients were eligible in this study. The median postoperative follow-up was 36 (7–115) months. The mean dose of pancreas was 4399.7 ± 396.0 cGy. The incidence of sarcopenia prior to CRT, at 6 months and 12 months later were 29.4% (45/153), 27.3% (35/128) and 37.0% (37/100). Both sarcopenia at 6 months (HR = 2.038, 95%CI = 1.084–3.833, P = 0.027) and sarcopenia at 12 months (HR = 2.216, 95%CI = 1.007–4.873, P = 0.048) were the independent prognostic factor of gastric cancer patients. V46 remained to be the only independent risk factor of sarcopenia at 6 months (OR = 3.889, 95%CI = 1.099–13.764, P = 0.035) and 12 months (OR = 6.067, 95% CI = 1.687–21.821, P = 0.006) in multivariate logistic regression analysis. Among the dosimetric parameters used for ROC analysis, the V46 showed the highest area under the curve (AUC = 0.707). Here is the relationship between sarcopenia rate and the cut-off value for V46. Higher sarcopenia rate at 6 months was noted in 42.6% patients with V46 ≥ 57% compared with 9% of patients with V46 < 57% (P < 0.001). The sarcopneia rate at 12 months was 52% with V46 ≥ 57% and 25% with V46 < 57% (P = 0.010).

Conclusion: Gastric cancer with sarcopenia after adjuvant CRT had poorer survival. Higher dose and larger irradiated volume of pancreas correlated with higher risk of sarcopenia. Appropriated administration of pancreas dose-volume may be conducive to reduce the risk of sarcopenia and improve survival in gastric cancer patients treated with adjuvant CRT.

1. Introduction

In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death [1]. Meanwhile, computer tomograph (CT) and Magnetic Resonance Imaging (MRI) have been proposed as gold standard for estimating muscle mass in researches [1].

Abbreviations: DVH, dose-volume histogram; CRT, adjuvant chemo-radiotherapy; SMI, skeletal muscle index; ROC, receiver operating characteristic; HR, hazard ratio; 95%CI, 95% confidence interval; OR, Odds ratio; AUC, area under the curve; IMRT, intensity-modulated radiation therapy; 3DCRT, three dimensional conformal radiation therapy; L3, the third lumbar vertebra.

* Corresponding author.
E-mail address: happyzhoufx@sina.com (F.-x. Zhou).

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Considerable attention has recently been paid to sarcopenia due to its association with shorter survival [2], increased chemotherapy toxicity [3] and post-operative complications [4]. Moreover, the high prevalence (15–60%) of sarcopenia in cancer patients has been described [5]. Among gastric cancer patients, the sarcopenia rate has been reported variously ranging from 12.5% to 58% [2,4,6–8].

Adjuvant abdominal concurrent chemoradiotherapy (CRT) can prolong survival and decrease recurrence for gastric cancer patients after radical surgery [9,10]. However, adjuvant abdominal CRT will cause injury to normal tissue (like pancreas, liver, gastrointestinal tract, kidney and so on) while it kills tumor cells. Radiation-induced malnutrition [11,12] is a common side effect of radiation therapy, and many patients suffer a acute or chronic gastrointestinal symptoms as a consequence. Recently, emerging studies have demonstrated that radiation can damage pancreas exocrine [13] and endocrine [14] function which play an important role in food digest and nutrition absorption. Therefore, we speculated that the irradiated pancreas might play an important role in sarcopenia for gastric cancer patients after adjuvant CRT. Up to now, there were little reports about this study. So the aim of this study is to evaluate the relationship between sarcopenia and pancreatic dose-volume in gastric cancer patients treated with adjuvant CRT after radical gastrectomy and provide more information for organ at risk (ORA) evaluation during relationship treatment planning.

2. Methods and materials

2.1. Patient eligibility and follow up

We retrospectively reviewed all the gastric cancer patients treated with adjuvant CRT after radical gastrectomy in Zhongnan Hospital of Wuhan University from January 2008 to December 2016. Inclusion criterions in this study were as follows: (1) the age ranged from 18 to 80; (2) available follow-up CT images prior to CRT, at 6 months and 12 months after CRT within 30 days respectively. Exclusion criteria: (1) serious metabolic disease such as diabetes, hyperthyroidism and decompensented cirrhosis; (2) distant metastasis; (3) intact or poor quality of imagines failed to identify skeletal muscle; (4) unfinished radiotherapy. The follow-up CT was initially performed within the first month after adjuvant CRT, and then every 3 months for 2 years, every 6 months to 5 years, and each year thereafter. All patients were followed until September 2017. This research was approved by Ethics committee of Zhongnan Hospital. The ethics approval ID is 2015047.

2.2. Treatment

All patients underwent CT-based radiation treatment planning. Bowel preparation had been done before CT simulation (200 ml water with urografin after 4 h empty stomach). Patients were immobilized in vacuum pad (klarity) during the CT scan. And the CT (SIEMENS Somatom Sensation Open 40) scan range was from 4 cm up to diaphragm muscle to the lower edge of fourth lumbar vertebrae with a slice thickness of 3 mm. Radiotherapy was administered by intensity-modulated radiation therapy (IMRT) or three dimensional conformal radiation therapy (3DCRT) technique, using 6-MV photons. During the treatment, almost the whole pancreas was irradiated. The protocol for treatment was referred to INT-0116 [9]. The treatment regions included the gastric bed, anastomosis and regional lymph nodes (gastric, celiac, gastroduodenal, porta hepatis, splenic, peripancreatic, pancreaticoduodenal and para-aortic A2B1 group). The prescription dose ranged from 45Gy to 50.5Gy which was delivered in 25 fractions (5 fractions per week for 5 weeks). The concurrent chemotherapy regimen was based on 5-fluorouracil (5-FU) (intravenous fluorouracil 400 mg/m^2 and leucovorin 200 mg/m^2 in the first 4 and the last 3 days of the radiotherapy).

2.3. Sarcopenia evaluating

A single slice of CT image of the third lumbar vertebra (L3) was selected for estimating muscle mass. After that, all images were imported into ImageJ software (The National Institutes of Health, Washington, MD, USA; version 1.47) to measure the area of the skeletal muscle mass of L3 (Fig. 1) [15]. Skeletal muscles were separated from other tissues through a Hounsfield Units (HU) threshold range from −29 to +150, and tissue boundaries were manually outlined if necessary. To minimize the measure bias, two investigators were trained to finish the measurement independently. The skeletal muscle index (SMI, cm^2/m^2) were computed by L3 skeletal muscle cross-sectional areas normalized for height (m^2).

2.4. Dose–volume relationship analysis

Almost all the pancreas had received 100% volume irradiation at the dose level of 30Gy. Therefore, the following pancreatic dose-volume metrics that derived from dose volume diagram (DVH) were evaluated in this study: V35, V40, V45, V46 and mean dose.

2.5. Statistics

Data was presented as mean ± standard derivation or percent frequency, unless otherwise specified. The cut-off value of sarcopenia was determined based on the log-rank method mentioned by Prado [6], that best separate the sarcopenic patients from those without according to time to an event outcomes (mortality). The group comparisons were conducted with student T test (normally distributed continuous data), Mann–Whitney U (abnormally distributed continuous data and ranked data) and $\chi 2$ tests (categorical data), respectively. Kaplan–Meier method was conducted to estimate the survival curves, and Log-rank test was applied to compare the differences between groups. Univariate analyses were performed to identify the potential risk factors associated with outcomes. Variables with a P-value <0.15 and clinical significance were included into subsequent multivariate (Logistic regression or Cox proportional hazards regression) analysis. The receiver

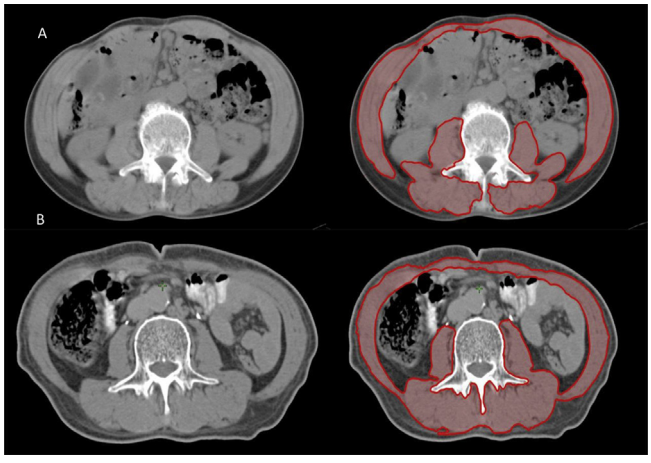

Fig. 1. Representative abdominal CT images obtained at the third lumbar vertebra (L3). Red zone indicates the muscle area identified using a Hounsfeld unit (HU) threshold of −29 to +150. Both patients (A, B) have similar BMI values (23.5 and 23.9 cm^2/m^2), but the former has a higher SMI (50.7 cm^2/m^2) than the latter (37.6 cm^2/m^2). (For interpretation of the references to color/colour in this figure legend, the reader is referred to the Web version of this article.)

operating characteristic (ROC) curve was applied to assess the predictability of pancreatic dosimetric parameters related to sarcopenia and determined the optimal cut-off value for each dosimetric parameter. And the incidences of sarcopenia between the two groups were estimated by $\chi 2$ tests. All tests were 2-sided and statistical significance was defined as a p value < 0.05. Statistical analysis was performed using SPSS20 (SPSS Inc.).

3. Results

3.1. Patient characteristics at baseline

There were 267 patients who undergoned with radiotherapy from January 2008 to December 2016. Among those patients, 114 patients were excluded as follows: 101 with unavailable CT imagines, 5 with hyperthyreosis, 3 with liver cirrhosis, 5 with diabetes. A total of 153 patients met our inclusion criteria for analysis. The selection process was shown in flow diagram (Fig. 2).

Baseline demographic and clinical characteristics listed in Table 1. The median age was 52.1 (26–80) years old, 101 (63.0%) was male. 103 (67.3%) patients were in clinical stage III. The median value of pre-SMI was 39.8 (23.7–60.0) cm^2/m^2. The sarcopenia rates prior to CRT, at 6 months and 12 months were 29.6% (45/152), 27.3% (35/128) and 37% (37/100). The clinical TNM stage was performed according to the AJCC of the 7th Edition TNM staging.

3.2. Prognostic value of sarcopenia

The median postoperative follow-up was 36 (7–115) months. During the follow-up, 55 (35.9%) persons died of cancer related event, and 16 (10.4%) patients lost contact. The cut-off value of sarcopenia was 40.2 cm^2/m^2 for male and 30 cm^2/m^2 for female, and it was determined based on the log-rank method mentioned by Prado [6], that best separate the sarcopenia patients from those without according to time to an event outcomes (mortality) [2,6,16]. The median survival time did not reach. Patient with sarcopenia at 6 months (P = 0.046) and 12 months (P = 0.038) had a lower survival than those without (Fig. 3).

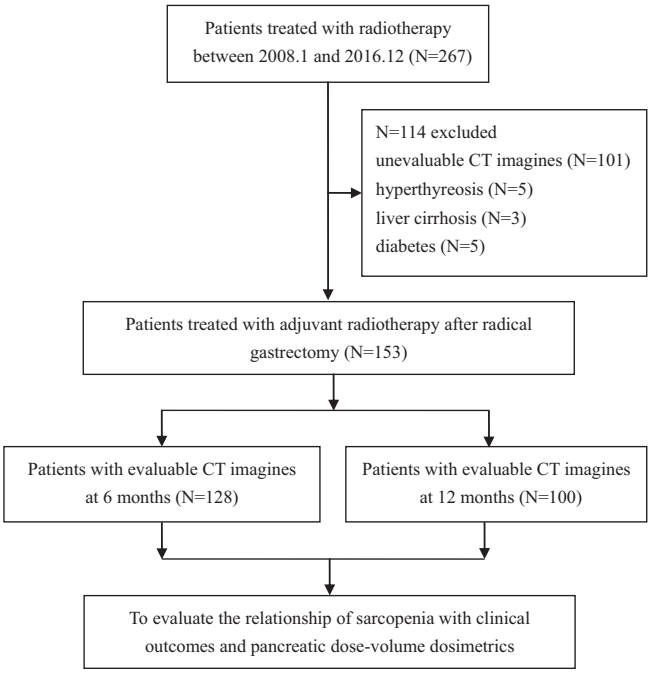

Fig. 2. Flow diagram of patients enrollment.

Table 1
Baseline demographics.

Characteristics	No. of patients (N = 153)
Age (years)	52.1 (26–80)
Sex	
M	101 (66.0%)
F	52 (34.0%)
Clinical stage	
I&II	50 (32.7%)
III	103 (67.3%)
Stage T	
T1	6 (3.9%)
T2	16 (10.5%)
T3	31 (20.2%)
T4	100 (65.4%)
Node	
N0	26 (17%)
N1	80 (52.3%)
N2	20 (13.2%)
N3	27 (17.5%)
Histological type	
Adenocarcinoma	122 (79.7%)
Others	31 (20.3%)
Operation	
D2[a]	97 (63.4%)
Non-D2	56 (36.6%)
Pre-SMI(cm^2/m^2)	39.8 ± 11.1
SMI at 6 month (cm^2/m^2)	40.4 ± 8.3
SMI at 12 month (cm^2/m^2)	38.2 ± 9.3
Pre-sarcopenia rate (%)	29.6% (45/152)
Sarcopenia rate at 6 month (%)	27.3% (35/128)
Sarcopenia rate at 12 month (%)	37% (37/100)
BMI (kg/m^2)	20.5 ± 3.07
BSA (m^2)	1.64 ± 0.14
Lumbar skeletal muscle index (cm^2/m^2)	40.8 ± 6.2
Serum Alb (g/l)	40.7 ± 5.9
Serum Hb (g/l)	108.9 ± 16.4
NRL	2.01 ± 0.6

NRL = neutrophil lymphocyte ratio; BMI = body mass index; BSA = body surface area; Alb = albumin; Hb = hemoglobin.
Data were expressed as n (%) or mean ± SD.
[a] D2 gastric operation means systematic dissection of lymph nodes in the first tier (perigastric) and the second tier (along the celiac artery and its branches).

Risk factors for overall survival were listed in Table 2. In the univariable COX analysis, the clinical stage (I & II VS III), sarcopenia at 6 months, sarcopenia at 12 months, chemotherapy cycles (≥6 VS < 6) were risk factors for overall survival, while the age (≥65 VS < 65), node (N0, N1, N2, N3), histological type (adenocarcioma VS others), tumor position (atrum, body, cardia), operation (D2 VS non-D2), operation (total gastectmoy VS others) or NRL (>2.4 VS ≤ 2.4) showed no statistic significance. After adjusting for age, clinical stage, node, chemotherapy cycles, D2 operation and sarcopenia at 6 months, the clinical stage (HR = 3.444, 95% CI = 1.527–7.768, P = 0.003), chemotherapy cycles less than 6 (HR = 2.557, 95%CI = 1.255–5.210, P = 0.010) and sarcopenia at 6 months (HR = 2.038, 95%CI = 1.084–3.833, P = 0.027) remained to be independent risk factor for overall survival. When the adjusting factors were age, clinical stage, node, chemotherapy cycles, D2 operation, sarcopenia at 12 months, the clinical stage (HR = 3.068, 95%CI = 1.051–8.956, P = 0.040) and sarcopenia at 12 months (HR = 2.216, 95%CI = 1.007–4.873, P = 0.048) turned out to be the independent risk factor.

3.3. Risk factors of sarcopenia

Clinical factors and dosimetrics comparisons between sarcopenia and non-sarcopenia were listed in Table 3, 4. Among the clinical

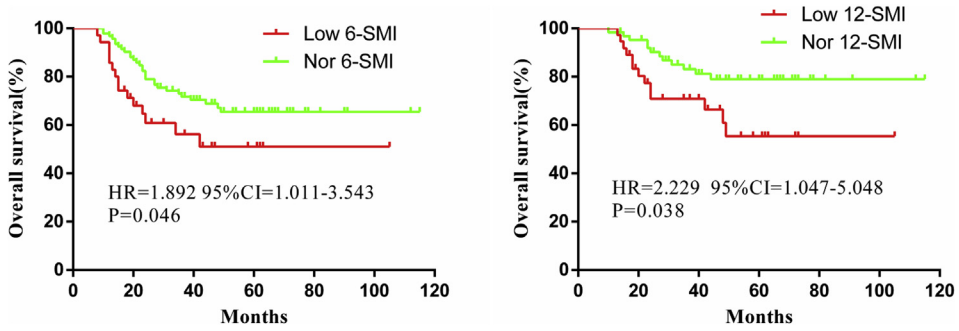

Fig. 3. Comparision of survival time between patients with or without sarcopenia at 6 months and 12 months.

Table 2
Univariate and multivariate analysis of factors associated with overall survival.

Clinicopathological characteristics	Univariable analysis			Multivariable analysis[b]			Multivariable analysis[c]		
	P	HR	95%CI	P	HR	95%CI	P	HR	95%CI
Age (≥65 VS <65)	0.151	1.623	0.838–3.144						
Node									
N0	0.076								
N1	0.481	1.333	0.600–2.961						
N2	0.965	0.977	0.339–2.818						
N3	0.035	2.492	1.065–5.831						
Clinical stage (I & II VS III)	**0.003**	2.842	1.431–5.648	**0.003**	3.444	1.527–7.768	**0.040**	3.068	1.051–8.956
Histological type (adenocarcioma VS others)	0.485	1.277	0.643–2.535						
Tumor position									
Atrum	0.426								
Body	0.377	0.638	0.236–1.727						
Cardia	0.800	1.152	0.386–3.438						
Operation (total gastectmoy VS others)	0.683	1.175	0.542–2.545						
Operation (D2 VS non-D2)[a]	0.313	1.318	0.771–2.252						
(Sarcopenia VS non) at 6 months	**0.046**	1.892	1.011–3.543	**0.027**	2.038	1.084–3.833			
(Sarcopenia VS non) at 12 months	**0.038**	2.229	1.047–5.048				**0.048**	2.216	1.007–4.873
Chemotherapy cycles (≥6 VS <6)	**0.040**	1.967	1.032–3.746	**0.010**	2.557	1.255–5.210			
NRL (> 2.4 VS ≤2.4)	0.285	1.508	0.710–3.205						

Bold indicates statistically significant.
NRL = neutrophil lymphocyte ratio.
[a] D2 gastric operation means systematic dissection of ymph nodes in the first tier (perigastric) and the second tier (along the celiac artery and its branches).
[b] Adjuting for age, clinical stage, node, chemotherapy cycles, operation (D2 VS non-D2), sarcopenia at 6 months.
[c] Adjusting for age, clinical stage, node, chemotherapy cycles, operation (D2 VS non-D2), sarcopenia at 12 months.

factors, no significant differences were observed in gender, age, node, clinical stage, histological type, D2 operation, gastrointestinal reaction, myelosuppression, anemia, hypoproteinemia and neutrophil lymphocyte ratio (NRL) (Table 3). As for the dosimetrics of pancreas, V46 showed a significant higher level in sarcopenia patients compared to those without (Table 4).

Risk factors for sarcopenia were showed in (Table 5). Multivariable analysis adjusting for age, clinical stage, tumor position, histological type, anemia, hypoalbuminemia, V46 and NLR, only V46 remained to be the independent predictor for sarcopenia at 12 months (OR = 6.067, 95%CI = 1.687–21.821, P = 0.006). When it comes to sarcopenia at 6 months, after controlling for age, clinical stage, histological-type, anemia, hypoalbunemia, V46, D2 operation, tumor differentiated and chemotherapy cycles, only V46 showed to be the only independent predictors (OR = 3.889, 95% CI = 1.099–13.764, P = 0.035).

3.4. Dose–volume relationship of pancreas and SMI

The mean dose of pancreas was 4399.7 ± 396.0 cGy. The lowest mean dose of pancreas in patients with sarcopenia at 6 months was 3471.2 cGy and 3785.2 cGy in those with sarcopenia at 12 months.

The area under the curve (AUC) results from ROC plots for V40, V45 and V46 of sarcopenia at 6 months were 0.634, 0.678 and 0.707, respectively. As for sarcopenia at 12 months, the AUC results for V40, V45 and V46 at 12 months were 0.588, 0.620 and 0.673, respectively. This result revealed that the best predictor of sarcopenia was V46. Figure 4 showed the predict ability of V46 for sarcopenia at 6 months (cut off value of V46 = 57%; AUC = 0.707, 95%CI = 0.614–0.789, P = 0.0001; sensitivity = 87.88%; specificity = 51.25%; positive predictive value = 43.57%; negative predictive value = 90.80%). The relationship between sarcopenia rate and cut-off value of V46 showed in Table 6. Higher sarcopenia rate at 6 months was noted in 42.6% patients with V46 ≥ 57% compared with 9% of patients with V46 < 57% (P < 0.001). The sarcopneia rate at 12 months was 52% with V46 ≥ 57% and 25% with V46 < 57% (P = 0.010).

4. Discussion

In this study, we clarify that gastric cancer patients treated with adjuvant CRT with sarcopenia at 6 and 12 months have poorer survival than those without. V46, pancreas dosemetric parameter, is the risk predictor for sarcopenia at 6 and 12 months. Higher dose and larger irradiated volume of pancreas is

Table 3
Relationship between sarcopenia and clinicopathological characteristics.

Characteristics	Sarcopenia at 6 months (N = 35)	Non-sarcopenia at 6 months (N = 93)	P	Sarcopenia at 12 months (N = 37)	Non-sarcopenia at 12 months (N = 63)	P
Gender						
Male	25 (71.4)	57 (61.3)	0.287[a]	21 (56.8)	42 (66.7)	0.322[a]
Female	10 (28.6)	36 (38.7)		16 (43.2)	21 (33.3)	
Age						
<65	31 (88.5)	84 (90.3)	0.992[b]	33 (89.2)	56 (88.9)	0.963[b]
≥65	4 (11.5)	9 (9.7)		4 (10.8)	7 (11.1)	
Node						
Positive	31 (88.6)	78 (83.9)	0.698[b]	34 (91.9)	51 (81.0)	0.234[b]
Negative	4 (11.4[c]	15 (16.1)		3 (8.1)	12 [c]19.0)	
Stage T						
T1	3 (9.0)	3 (3.2)	0.936[c]	2 (5.4)	4 (6.3)	0.371[c]
T2	3 (9.0)	12 (12.9)		4 (10.8)	8 (12.7)	
T3	7 (20.0)	20 (21.5)		5 (13.5)	13 (20.6)	
T4	22 (62.0)	58 (62.4)		26 (70.3)	38 (60.4)	
Stage TNM						
I&II	10 (28.6)	31 (33.3)	0.607[a]	10 (27.0)	24 (38.0)	0.259[a]
III	25 (71.4)	62 (66.7)		27 (73.0)	39 (62.0)	
Histologicaltype						
Adenocarcinoma	32 (91.4)	71 (76.3)	0.108[b]	32 (86.5)	48 (76.2)	0.200[e]
Others	3 (8.6)	22 (23.7)		5 (13.5)	15 (23.8)	
Operation						
D2[b]	24 (68.6)	59 (63.4)	0.588[a]	24 (64.9)	43 (68.3)	0.391[a]
Non-D2	11 (31.4)	34 (36.6)		13 (35.1)	20 (31.7)	
GR						
I & II	29 (82.9)	82 (88.1)	0.430[a]	32 (86.5)	55 (87.3)	0.907[a]
III & IV	6 (17.1)	11 (11.8)		5 (13.5)	8 (12.7)	
Myelosuppression						
I & II	24 (68.6)	74 (75.5)	0.109[a]	25 (33.8)	49 (66.2)	0.261[a]
III & IV	11 (31.4)	19 (63.3)		12 (46.2)	14 (53.8)	
BSA (m^2)	1.65 ± 0.16	1.62 ± 0.14	0.308[d]	1.63 ± 0.16	1.64 ± 0.13	0.758[d]
SMI (cm^2/m^2)	33.0 ± 5.6	43.1 ± 7.3	**0.001**[d]	30.0 ± 6.7	43.0 ± 6.8	**0.001**[d]
Alb (g/l)	39.6 ± 3.0	41.8 ± 4.4	0.125[d]	40.0 ± 3.4	41.7 ± 4.1	0.085[d]
Hb (g/l)	106.8 ± 16.7	109.8 ± 15.9	0.440[d]	107.4 ± 18.6	110.0 ± 15.7	0.459[d]
NRL	106.8 ± 16.7	109.8 ± 15.9	0.440[d]	107.4 ± 18.6	110.0 ± 15.7	0.459[d]

Bold indicates statistically significant.
NRL = neutrophil lymphocyte ratio; BMI = body mass index; BSA = body surface area; SMI = skeletal muscle index; GR = gastrointestinal reaction; Alb = albumin; Hb = hemoglobin.
Data were expressed as n (%) or mean ± SD.
[a] Pearson Chi–Square test.
[b] continuity correction.
[c] Kruskal–Wallis Test.
[d] Student t test.
[e] D2 gastric operation means systematic dissection of lymph nodes in the first tier (perigastric) and the second tier (along the celiac artery and its branches).

correlated with higher sarcopenic rate. Appropriated administration of pancreas dose may be conducive to reduce the risk of sarcopenia and improve prognosis in gastric cancer patients treated with adjuvant CRT.

Accumulating evidences have demonstrated that sarcopenia is associated with adverse clinical outcomes [2,4]. Our study showed that gastric cancer patients with sarcopenia at 6 and 12 months had poorer overall survival (OS). This result was agreed with the study by Cheng L aimed the relationship between sarcopenia (HR = 1.653, P < 0.001) and long time survival in gastric cancer patients after radical gastrectomy [2]. However, the underlying mechanism remained unclear. Reasons as following may be hypothesized. Firstly, sarcopenic patients are more physical inactivity and more susceptible to severe postoperative complications [4]. It is known for us that higher postoperative complications is associate with lower survival [17]. Secondly, previous researches have demonstrated that sarcopenic patients have lower tolerance for adjuvant chemotherapy [3], since adjuvant chemotherapy is a strong protect factor for tumor control and overall survival [18]. Thirdly, sarcopenia is related to the weaken immune system of

Table 4
Comparison of pancreas dosimetrics between sarcopenia and non-sarcopenia patients.

Pancreas dosimetrics	Sarcopenia at 6 months (N = 35)	Non-sarcopenia at 6 months (N = 93)	P	Sarcopenia at 12 months (N = 37)	Non-sarcopenia at 12 months (N = 63)	P
Mean Dose (cGy)	4343.1 ± 262.2	4423.7 ± 280.1	0.551	4390.0 ± 372.3	4364.9 ± 397.6	0.460
V35 (%)	85.7 ± 9.4	82.3 ± 11.5	0.160	83.4 ± 11.0	80.1 ± 9.0	0.266
V40 (%)	82.2 ± 9.2	76.2 ± 10.0	**0.025**	78.5 ± 10.1	74.6 ± 9.1	0.161
V45 (%)	77.9 ± 8.1	68.7 ± 8.9	**0.003**	73.1 ± 8.1	67.0 ± 9.7	0.057
V46 (%)	72.7 ± 7.9	60.5 ± 8.6	**0.001**	67.9 ± 8.0	57.8 ± 9.0	**0.006**

Bold indicates statistically significant.
Kruskal–Wallis Test.

Table 5
Multivariable Logistic regression analysis of risk factors with sarcopenia at 6 and 12 months.

Variables	Sarcopenia at 12 months (N = 128)			Sarcopenia at 6 months (N = 100)		
	OR	P	95%CI	OR	P	95%CI
Age	1.471	0.750	1.232–15.854	1.343	0.788	0.157–11.508
Clinical stage	1.272	0.768	0.257–6.292	2.364	0.361	0.374–14.951
Tumor position	0.672	0.410	0.261–1.728	–	–	–
Histologicaltype	0.393	0.409	0.043–3.610	0.194	0.170	0.019–2.018
Anemia	0.546	0.526	0.065–4.235	0.749	0.831	0.053–10.656
Hypoalbuminemia	0.999	0.999	0.201–4.958	0.979	0.984	0.119–8.045
V46	6.067	**0.006**	1.687–21.821	3.889	**0.035**	1.099–13.764
NLR	0.288	0.088	0.069–1.202	–	–	–
D2 operation[a]	–	–	–	1.250	0.805	0.212–7.376
Differentiated	–	–	–	5.929	0.055	0.963–36.497
Chemotherapy cycle	–	–	–	2.377	0.541	0.148–38.119

Bold indicates statistically significant.
GR = gastrointestinal reaction; NRL = neutrophil lymphocyte Ratio.
[a] D2 gastric operation means systematic dissection of lymph nodes in the first tier (perigastric) and the second tier (along the celiac artery and its branches).

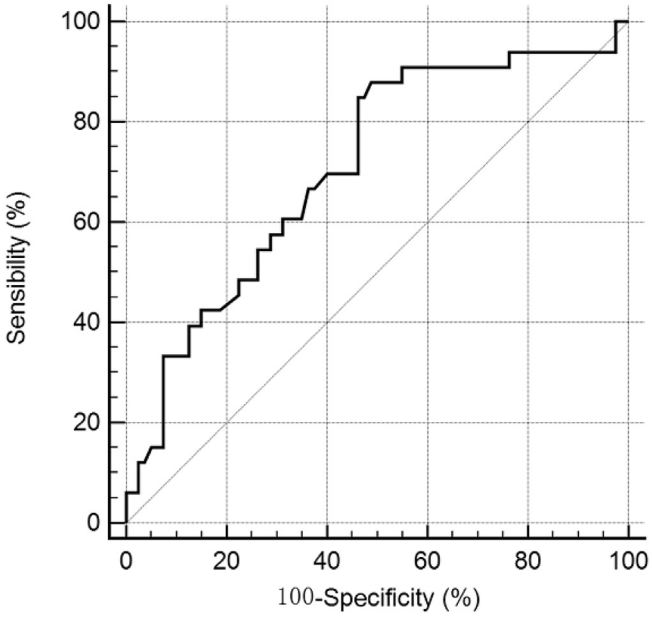

Fig. 4. ROC curve using sarcopenia at 6 months as dependent variable and V46 as independent variable. The cut off value was 57%. AUC = 0.707 (95%CI = 0.614–0.789, P = 0.0001), sensitivity = 87.88%, specificity = 51.25%, positive predictive value = 43.57%, negative predictive value = 90.80%. ROC = receiver operating characteristic; V46 = the pancreas volume receiving more than 46Gy; AUC = area under the curve.

the host, and it may be a reflection of a more aggressive tumor biology with increased metabolic activity [19]. At last, the study by Bente K indicated that muscle cell is a secretory organ which may influence cancer cell growth and pancreas function [20]. He speculated that skeletal muscle might mediate some of the well-established protective effects of exercise via secretion of proteins that could counteract the harmful effects of proinflammatory adipokines [20].

Regarding to the risk factors of sarcopenia, no common consensus had been reached. It has been reported that sarcopenia patients usually have a lower level of BMI, NRS 2002 score, serum albumin and hemoglobin [2,4,7]. However, the leading role in the development of sarcopenia still remains unclear. In our study, V46 remained to be the only independent risk factor of sarcopenia in logistic analysis after adjusting for pancreas dose-volume metrics and clinical risk factors. There were reports, however, of functional (endocrine and exocrine) and histological abnormalities occurring after abdominal irradiation in both animals and human [13,14,21–24], which palys an important role in patients' nutrition status. In addition, sarcopenia or cachexia can frequently be seen in some patients undergone abdominal radiation [25], especially those with severe weight loss, fatigue weakness, diarrhea and so on [24]. In short, it is a reasonable speculation that the radiation-induced pancreas injury increased the sarcopenia rate.

As far as we know, the dose-volume effects of pancreas radiation have not been fully elucidated. From the beginning of 1996, there were lots of animal studies aimed at the effect of radiation-induced injury on pancreas' histological and endocrine and exocrine functional, with most of the dose level concentrated on 40–50Gy [21,22,26]. Histological abnormalities of the entire pancreas organ–acinar cell necrosis, mild injury of the duct cells, atrophy of the ductules, vascular lesions and delayed diffuse fibrosis–had been observed. What's important, almost all the animals had been found exocrine pancreatic insufficiency, espeically in the early stage of radiation, and radiation-induced pancreas injury was permanent in some animals. In 1993, a study [24] aimed at the relationship of chronic pancreatitis and abdominal radiotherapy, including five patient with nonalcoholic chronic pancreatitis who undergone abdominal radiotherapy for Hodgkin's disease (n = 4) or seminoma (n = 1) at dose ranging from 3600 to 4050 rads, 6–20 years (median, 7 years) before the onset of pancreatitis. It had been found that most patients suffered from pancreatic pain, steatorrhea and diabetes mellitus. They concluded that abdominal radiotherapy should be added to the list of causes of chronic pancreatitis and vascular process should responsible for the hysiopathology of post-

Table 6
Comparison of sarcopenia rate for each pancreas dosimetrics.

Dosimetrics parameter	Cut-off	Sarcopenia rate at 6 months	P	AUC	Cut-off	Sarcopenia rate at 12 months	P	AUC
V46 (%)	≥57	42.6%	<**0.001**	0.707	≥57	52%	**0.010**	0.673
	<57	9%			<57	25%		

AUC = area under the curve.
X^2 test.

radiation chronic pancreatitis. The research by Jerzy Wydmanski [13] evaluated the radiation-induced injury of the exocrine pancreas among 127 gastric cancer patients with a total dose of 45 Gy given in 25 fractions. Lipase and a-amylase deficiencies were found in 48.2% and 19.7% patients respectively. It suggested that CRT increased the risk of exocrine pancreatic insufficiency in gastric cancer patients and the pancreas should be taken as OAR (organ at risk). Hence, we conclude that 46Gy, the pancreas irradiation dose, is enough to induce pancreas functional and histological abnormalities. Furtherly, it had been reported that muscle loss was associated with metabolic abnormalities accompanying with increased production of cytokines, such as interleukin (IL)-1β, IL-6, interferon-γ, and tumor necrosis factor (TNF)-α [27,28]. What's interesting, radiation-induced pancreas injury can enhance the release of cytokines as well, which mediated a series of pathophysiological responses [29]. A reasonable explanation is that the increased sarcopenia rate mediated by radiation-induced pancreas injury might promoted by the proinflammatory cytokines and the systemic inflammatory reaction.

To the best of our knowledge, this study provides the first evidence for the association between pancreatic dose-volume and sarcopenia rate. In our investigation, we determined optimal cut-off value using ROC curves for the pancreatic dosimetric parameter. Higher sarcopenia rate at 6 months was noted in 42.6% patients with V46 $\geq$ 57% compared with 9% of patients with V46 < 57% ($P < 0.001$). The sarcopneia rate at 12 months was 52% with V46 $\geq$ 57% and 25% with V46 < 57% ($P = 0.010$). This result revealed that higher dose and larger irradiated volume of pancreas correlated with higher risk of sarcopenia rate. Previous researches have indicated that sarcopenia may be a therapy target for cancer patients [30]. Protein supplementation [31], resistance exercise [32,33] and vitamin D [34] have been proposed as the treatment of sarcopenia according to Society for Sarcopenia, Cachexia, and Wasting Disease (SCWD). However, those methods have limited effectiveness. Our findings may provide a new potential method for sarcopenia through the appropriated administration of pancreas dose in gastric cancer patient treated with adjuvant CRT.

This study has several limitations. Firstly, The EWGSOP has proposed both muscle strength and muscle mass as a diagnostic standard for sarcopenia. Muscle mass alone was measured due to a respective study. Secondly, this was a single-center retrospective observational study and the sample size was small. A validation and prospective study with larger sample size is necessary to confirm the pancreatic dose-volume effects on sarcopenia. Nonetheless, our study has provided important information about the relationship between the pancreatic dose-volume metrics and sarcopenia in gastric cancer patients treated with adjuvant CRT.

5. Conclusion

Gastric cancer patients undergone adjuvant chemoradiotherapy with sarcopenia had a poorer OS. V46 was the independent risk factor for sarcopenia. Higher dose and larger irradiated volume of pancreas correlated with higher risk of sarcopenia. We proposed that appropriate dose limits (V46 $\leq$ 57%) for pancreas may be conducive to reduce the risk of sarcopenia and improve survival in gastric cancer patients undergone adjuvant CRT.

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Conflict of interest

The authors declare no conflict of interest.

Acknowledgment and Author contributions

Study Design: Fu-xiang Zhou, Yi Li.

Data Collection: Yi Li, Ji Chen, Yan Gao, Jing Dai, Jin Peng, Ling Xia.

Data Analysis: Yi Li, Wen-bo Wang, Huan-gang Jiang.

Data Interpretation: Yi Li, Zheng-kai Liao, Yun-feng Zhou, Fu-xiang Zhou.

Writing of Manuscript: Yi Li, Wen-bo Wang, Huan-gang Jiang.

Critical Revision: Yi Li, Fu-xiang Zhou, Yun-feng Zhou, Cong-hua Xie.

Final Approval: Yi Li, Yun-feng Zhou, Fu-xiang Zhou.

Overall Supervision: Fu-xiang Zhou.

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