



# Quantitative CT measurement of left colonic and pelvic mesenteric adipose volume in radiation proctitis

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**Background:** The edema of left colonic and pelvic mesenteric adipose tissues has long been recognized in surgery as a characteristic feature of radiation proctitis (RP). However, the correlation between mesenteric adipose volume and RP has not been extensively clarified. The purpose of this study was thus to assess the variation of left colonic and pelvic mesenteric adipose volume in RP.

**Methods:** From March 2013 to June 2015, the data of 52 patients with locally advanced rectal cancer who underwent neoadjuvant chemoradiotherapy, including 23 patients with RP and 29 with non-RP (nRP), were retrieved. The mesenteric adipose volume was quantified via a computed tomography (CT) reconstruction method. Corresponding analyses were conducted to observe the correlation between the relative change of mesenteric adipose volume and the thickening degree of the rectal wall.

**Results:** The baseline data of the RP group and the nRP group were comparable. There was no significant difference in the relative change of the left colonic mesenteric adipose volume in each vertebral space from the third lumbar vertebra to the first sacral vertebra before and after radiotherapy. The relative change of pelvic mesenteric adipose volume ( $\Delta V_p\%$ ) was notably higher in the RP group compared to the nRP group. With a  $\Delta V_p\%$  cutoff value of 3.67%, the sensitivity and specificity for the diagnosis of RP were 65.2% and 86.2%, respectively. According to the correlation analysis,  $\Delta V_p\%$  in the RP group was significantly correlated with the thickening degree of the rectal wall after radiotherapy ( $r=0.47$ ,  $P=0.024$ ).

**Conclusions:** The increment of the relative change of pelvic mesenteric adipose volume quantitatively measured by CT can be clinically useful in identifying RP.

**Keywords:** Radiation proctitis (RP); neoadjuvant chemoradiotherapy; mesenteric adipose volume; anastomotic leakage

Submitted Jun 09, 2020. Accepted for publication Jul 14, 2020.

doi: 10.21037/atm-20-5102

View this article at: <http://dx.doi.org/10.21037/atm-20-5102>

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## Introduction

Preoperative radiotherapy combined with concurrent chemotherapy is the standard neoadjuvant regimen for locally advanced rectal cancer (LARC) (1). Studies have demonstrated neoadjuvant chemoradiotherapy can reduce the tumor stage, prevent local recurrence, and improve the rate of anus preservation (2,3). But these advances have not markedly decreased the risk of distant metastasis, which remains the leading cause of death for LARC. Recently, multiple trials have reported promising outcomes on the use of total neoadjuvant therapy (TNT), incorporating both chemotherapy and radiotherapy in the preoperative setting. With improved treatment compliance and reduced toxicities, TNT increases the pathologic complete response rate and facilitates patients who are eligible for organ preservation, potentially increases distant control and long-term survival for patients with LARC (4-7).

However, there are potential disadvantages after neoadjuvant chemoradiotherapy. The delay in definitive surgery could allow for local disease progression, particularly in those patients who do not respond to neoadjuvant treatment. Neoadjuvant chemoradiotherapy may impact the performance status of patients who undergo planned surgery, which potentially increase postoperative complications. Higher grade 3 to 4 radiation dermatitis, hematologic, and gastrointestinal toxic effects were observed in patients who received radiotherapy (8-10). Radiation proctitis (RP), caused by preoperative radiotherapy, can profoundly reduce the patients' anal functions and quality of life (11-13). Randomized controlled trials and post hoc analyses have shown that preoperative radiotherapy greatly increases the incidence of anastomotic leakage, and that RP manifest in preoperative imaging is an independent risk factor for anastomotic leakage (8,14).

RP is an inflammatory bowel disease diagnosed through a combination of clinical, endoscopic, and imaging measures. The most common and bothersome complaint from RP patients is rectal bleeding. Other symptoms include anal pain, diarrhea, urgency, and incontinence (15). Endoscopic biopsy is performed for differential diagnosis and to rule out other causes of chronic proctitis (16). Surgical assessment of RP often reveals that the mesentery is edematous and thickened, but the relevance of these features has yet to be determined.

The previous study investigated the effect of radiation-induced injury on anastomosis from pathological view and found that RP had a more severe microvascular injury (17). Preoperative evaluation of RP is helpful to identify patients

at high risks of anastomotic leakage. Computed tomography (CT) occupies an important role in evaluating bowel radiation injury, and typical CT manifestations include thickening of the rectal wall and edema of mesenteric adipose tissues. To the best of our knowledge, there is no unified quantitative standard to evaluate the change of mesenteric adipose in RP. The purposes of this study were thus to quantitatively measure the variation of left colonic and pelvic mesenteric adipose volume after radiotherapy, to analyze its correlation with the thickening degree of the rectal wall, and to evaluate the ability of mesenteric adipose volume changes to identify RP.

We present the following article in accordance with the MDAR reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-5102>).

## Methods

### *Patients*

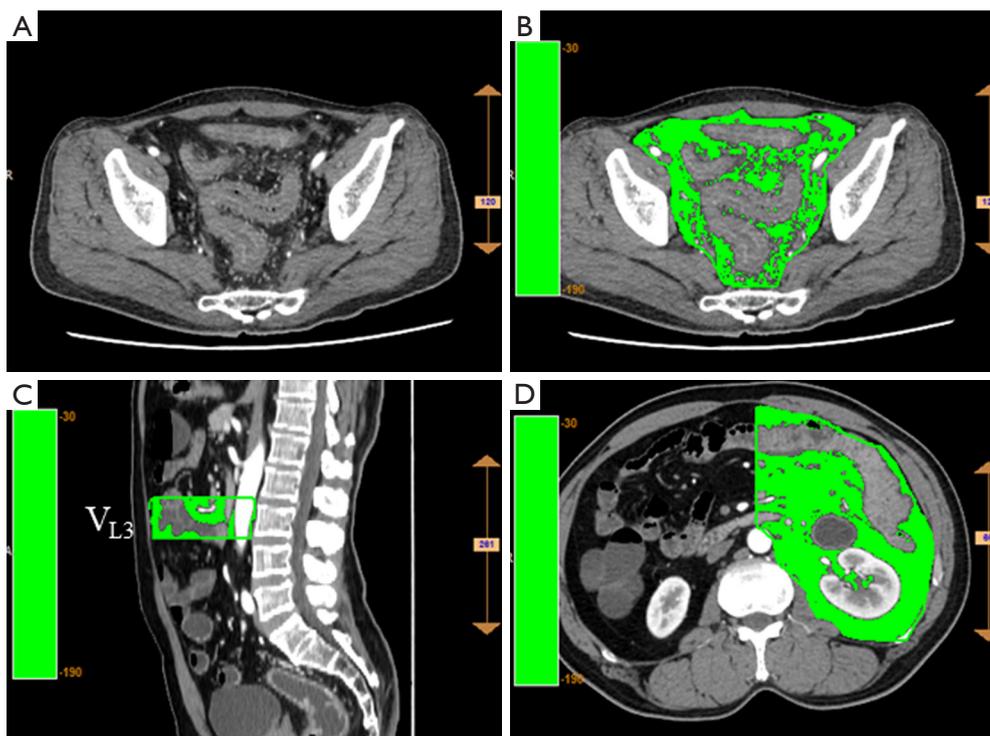
From March 2013 to June 2015, the data from patients with locally advanced rectal cancer who were enrolled in an open-label, multicenter, three-arm randomized controlled trial (FOWARC study, NCT01211210) at the Sixth Affiliated Hospital of Sun Yat-sen University for neoadjuvant chemoradiotherapy were retrieved. The detailed protocol has been published elsewhere (8).

Inclusion criteria in this study were patients who received a total dose of 46.0–50.4 Gy administered 5 times weekly in 25 to 28 daily fractions, along with concurrent fluorouracil-based chemotherapy; patients who underwent radical operation for rectal cancer 4 to 6 weeks after chemoradiotherapy; and patients with complete abdominal and pelvic enhanced CT image data before and after radiotherapy. Meanwhile, patients with incomplete CT images, including those whose original data were broken or unavailable, were excluded.

Ethical approval and patient informed consent are waived as we analyzed the CT images retrospectively, without any interventions or hazard to patients.

### *Diagnosis of RP*

RP was diagnosed by clinical history, preoperative colonoscopy, and radiologic investigation. Endoscopic manifestations include telangiectasia, diffuse mucosal edema, ulcer, bowel stenosis, and stiffness. The main manifestations of pelvic magnetic resonance imaging (MRI)



**Figure 1** Measurement of left colonic and pelvic mesenteric adipose volume. Pelvic enhanced CT showed that the rectal wall was dramatically thickened after radiotherapy (A). The pelvic mesenteric adipose volume was measured by axial imaging (B). The left colonic mesenteric adipose volume was measured by sagittal (C) and axial (D) imaging in each vertebral space.

are edema and circumferential thickening of the rectal wall, accompanied by stratification effect, edema of the mesentery and surrounding pelvic soft tissues, and similar tissue changes of the distal sigmoid colon within the scope of radiotherapy (14,18).

### **CT protocols**

CT images were obtained through the Toshiba Aquilion ONE 128-detector CT scanner. The scanning range was from the lower third of the heart to the pubic symphysis. The tube voltage was 120 KV, and the tube current was 330 mAs. The contrast agent was injected through the cubital vein with an injection flow rate of 3.0 mL/s for enhanced scanning. All slides were reconstructed into images with 3 mm layer thickness and 3 mm layer spacing.

### **Measurement of left colonic and pelvic mesenteric adipose volume**

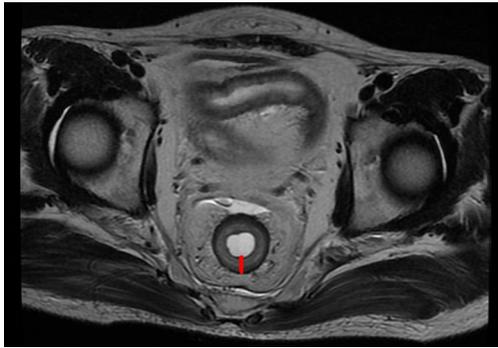
The reconstructed images were analyzed according to

the ANYTHINK GVCM system (CREALIFE Medical Technology, Beijing, China). The left colonic mesenteric adipose volume was measured in each vertebral space from the third lumbar vertebra to the first sacral vertebra (L3 to S1). The upper boundary of the pelvic mesenteric adipose volume was at the level of the S1 vertebra, and the lower boundary was at the hiatus of the levator ani muscle (*Figure 1*).

All measurements were performed by the same senior physician. To ensure blinding, the grouping information of the patients was not divulged before measurement.

### **Measurement of rectal wall thickness**

Pelvic MRI was used to measure the thickness of the rectal wall without tumor (*Figure 2*). All of the recruited patients received an initial MRI scan before treatment for tumor staging and a second MRI scan after completion of neoadjuvant chemoradiotherapy. The MRI protocols and measurement have been reported previously (19). The data on rectal wall thickness was collected from the RP database for analysis.



**Figure 2** The thickness of rectal wall without tumor was measured by axial T2 imaging at its widest point.

### Statistics

Continuous data are represented as “ $\bar{x} \pm s$ ”, and categorical data as proportions (percentage). The Student’s *t*-test was applied to evaluate the differences in continuous variables depending on the normality of the data distribution. The Chi-square test or Fisher’s exact test was utilized to evaluate differences in categorical variables, as appropriate. A two-sided Pearson’s test was adopted for correlation regression analysis. SPSS 19.0 software (IBM Corp., Armonk, NY, USA) was employed for analysis. Differences were proven statistically significant if the P value was  $<0.05$ .

For evaluation, the relative change of mesenteric adipose volume ( $\Delta V\%$ ) was defined as follows: (mesenteric adipose volume after chemoradiotherapy – mesenteric adipose volume before chemoradiotherapy)/mesenteric adipose volume before chemoradiotherapy  $\times 100\%$ . The relative change of rectal wall thickness ( $\Delta L\%$ ) was calculated as follows: (rectal wall thickness after chemoradiotherapy – rectal wall thickness before chemoradiotherapy)/rectal wall thickness before chemoradiotherapy  $\times 100\%$ .

## Results

### Patient characteristics

A total of 52 patients were recruited in this study, including 23 cases of RP (RP group) and 29 cases of non-RP (nRP group). The patients in the RP group tended to have more anastomotic leakage (both clinical and subclinical leaks) than those in the nRP group [34.8% (8/23) *vs.* 13.8% (4/29),  $P=0.07$ ]. The rate of anastomotic stenosis was considerably higher in the RP group than in the nRP group [30.4% (7/23) *vs.* 3.4% (1/29),  $P=0.02$ ]. The other clinical characteristics between the two groups were comparable (Table 1).

### CT measurement

Table 2 presents the left colonic and pelvic mesenteric adipose volume measurement results. There was no significant difference in the left colonic mesenteric adipose volume before and after neoadjuvant radiotherapy in each vertebral space from L3 to S1 between the two groups, neither was the pelvic mesenteric adipose volume. Concerning the relative change of mesenteric adipose volume, the increment of the relative change of pelvic mesenteric adipose volume ( $\Delta V_p\%$ ) was greater in the RP group than in the nRP group ( $P=0.001$ ).

### Predictive value of $\Delta V_p\%$ in RP

The  $\Delta V_p\%$  was additionally introduced into the receiver operating characteristic (ROC) curve to evaluate the predictive value for RP (Figure 3). The area under the curve (AUC) was 0.765, which displayed a significant value in differentiating RP from nRP ( $P<0.001$ ). With a cutoff value of 3.67%, the sensitivity and specificity for the diagnosis of RP were 65.2% and 86.2%, respectively.

### Correlation between $\Delta V_p\%$ and $\Delta L\%$

The maximum diameter of the rectal wall thickness of the two groups, not including the location of the tumor, was measured on the T2 axial image of the pelvic MRI before and after radiotherapy (Table 3). After radiotherapy, the thickness of the rectal wall was markedly increased in the RP group. The relative change of rectal wall thickness ( $\Delta L\%$ ) was more observable in the RP group than in the nRP group ( $P<0.01$ ).

$\Delta V_p\%$  and  $\Delta L\%$  were additionally included in the correlation analysis. The correlation coefficient in the RP group of 0.47 and the two-sided Pearson’s test outcome of  $P=0.024$  implied that  $\Delta V_p\%$  was notably correlated with  $\Delta L\%$ , whereas there was no statistically observable correlation in the nRP group ( $r=0.02$ ,  $P=0.922$ ) (Figure 4).

## Discussion

RP is a common consequence of radiation therapy for pelvic malignancies (20,21). Efforts have been made to specifically prevent, diagnose, and manage its adverse effects (22). However, no gold standard exists for RP diagnosis. In the present study, the left colonic and pelvic mesenteric adipose volume were quantitatively measured, and their relation to

**Table 1** Comparison of the clinical characteristics between the RP and nRP groups

Variable	RP group (n=23)	nRP group (n=29)	P
Gender (n, %)			0.57
Male	16 (69.6)	18 (62.1)	
Female	7 (30.4)	11 (37.9)	
Age (y, $\bar{x} \pm s$ )	51.4 $\pm$ 13.6	55.5 $\pm$ 10.8	0.22
ASA score (n, %)			0.53
1	4 (17.4)	3 (10.3)	
2	19 (82.6)	25 (86.2)	
3	0	1 (3.4)	
BMI (kg/m <sup>2</sup> , $\bar{x} \pm s$ )			
Before radiotherapy	22.5 $\pm$ 3.7	23.3 $\pm$ 3.0	0.43
After radiotherapy	21.6 $\pm$ 3.0	22.3 $\pm$ 3.0	0.39
Tumor size (cm, $\bar{x} \pm s$ )	2.4 $\pm$ 1.4	2.1 $\pm$ 1.0	0.34
Distance of tumor from anal verge (cm, $\bar{x} \pm s$ )	6.6 $\pm$ 2.3	6.5 $\pm$ 2.8	0.96
Tumor stage (n, %)			0.26
II	6 (26.1)	3 (10.3)	
III	17 (73.9)	26 (89.7)	
Chemotherapy plan (n, %)			0.78
5-Fu	12 (52.2)	14 (48.3)	
mFOLFOX6	11 (47.8)	15 (51.7)	
Full dose of radiotherapy (n, %)			1.0
Yes	23 (100.0)	28 (96.6)	
No	0	1 (3.4)	
Anastomotic leakage (n, %)	8 (34.8)	4 (13.8)	0.07
Anastomotic stenosis (n, %)	7 (30.4)	1 (3.4)	0.02

RP, radiation proctitis; nRP, non-RP.

RP was analyzed. The  $\Delta V_p\%$  was dramatically higher in the RP group, with a favorable sensitivity and specificity in predicting RP. Moreover,  $\Delta V_p\%$  and  $\Delta L\%$  were highly correlated. For patients undergoing neoadjuvant chemoradiotherapy,  $\Delta V_p\%$  could be regarded as a useful predictor of RP.

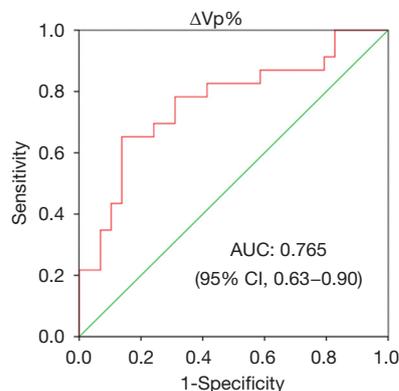
The mesentery is considered to be an independent organ, and thus its function and role in various diseases have become issues of intense research interest (23,24). Histological study has confirmed that the epithelial cells and connective tissue of the mesentery are continuous with the intestinal wall (25). The abnormalities of mesenteric adipose

tissue morphology and function are closely bound up with the occurrence and development of various diseases (26-28). In RP, when the pelvic mesentery is exposed to radiation, it is inevitably injured. The mesentery may appear to present such imaging changes as edema, increased density, thickening of mesenteric vessels, and blurred margin after radiotherapy. As far as we know, few if any studies have investigated the relationship between mesenteric adipose volume and radiation injury. We therefore believe that the present study is the first to use CT to quantitatively measure the mesenteric adipose volume before and after radiotherapy. All measurements of this study were

**Table 2** The left colonic and pelvic mesenteric adipose volume measured by CT

Variable	RP group (n=23)	nRP group (n=29)	P
Preradiotherapy			
$V_{L3}$ (mL, $\bar{x} \pm s$ )	390.7±123.9	410.0±126.7	0.58
$V_{L4}$ (mL, $\bar{x} \pm s$ )	340.0±102.4	346.1±105.5	0.84
$V_{L5}$ (mL, $\bar{x} \pm s$ )	291.0±84.1	289.9±88.6	0.96
$V_{S1}$ (mL, $\bar{x} \pm s$ )	88.9±22.0	92.1±31.5	0.69
$V_p$ (mL, $\bar{x} \pm s$ )	1,304.2±176.7	1,450.4±359.7	0.08
Postradiotherapy			
$V_{L3}$ (mL, $\bar{x} \pm s$ )	402.9±106.8	400.5±130.1	0.94
$V_{L4}$ (mL, $\bar{x} \pm s$ )	341.1±80.6	328.5±106.9	0.64
$V_{L5}$ (mL, $\bar{x} \pm s$ )	292.6±79.5	273.3±93.1	0.43
$V_{S1}$ (mL, $\bar{x} \pm s$ )	94.7±31.6	90.6±32.5	0.65
$V_p$ (mL, $\bar{x} \pm s$ )	1,344.6±210.7	1,385.4±321.6	0.60
Relative change			
$\Delta V_{L3}\%$	5.1±13.9	-1.3±15.4	0.12
$\Delta V_{L4}\%$	4.0±21.9	-4.5±14.2	0.10
$\Delta V_{L5}\%$	2.2±15.3	-5.9±14.7	0.06
$\Delta V_{S1}\%$	6.7±21.0	0.94±25.3	0.38
$\Delta V_p\%$	3.0±6.9	-3.8±7.1	0.001

RP, radiation proctitis; nRP, non-RP.  $V_{L3}$ - $V_{S1}$ , mesenteric adipose volume in each vertebral space from L3 to S1;  $V_p$ , pelvic mesenteric adipose volume.



**Figure 3** ROC curve showing the predictive value of  $\Delta V_p\%$  for radiation proctitis.  $\Delta V_p\%$ , the relative change of pelvic mesenteric adipose volume; AUC, area under the curve.

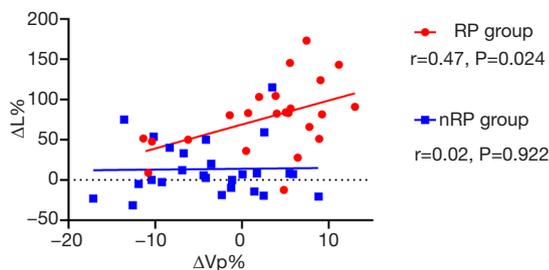
performed by the same senior physician to control bias. We discovered that  $\Delta V_p\%$  had a fair ability to predict RP. While there was no prominent difference in pelvic

mesenteric adipose volume before and after radiotherapy between the RP group and the nRP group,  $\Delta V_p\%$  in the RP group was markedly higher than that in the nRP group. The decrease of  $\Delta V_p\%$  in the nRP group may be related to the reduction in body mass index (BMI). Owing to the influence of long-course chemoradiotherapy and tumor burden, most patients experience a decline in BMI after a short period of time. Also, the intestinal symptoms may put patients under extreme psychological pressure, significantly reducing their food intake, and eventually increasing the incidence of malnutrition in radiation enteritis patients (29). Therefore, more attention should be paid to the nutrition of radiotherapy patients. Second, the left colonic mesenteric adipose volume in each vertebral space from L3 to S1 showed no difference across the RP and nRP groups. This indicates that the effect of radiotherapy for locally advanced rectal cancer on the mesentery was mainly below the S1 plane of the pelvis. As the previous study suggested, part of the sigmoid colon, which can be used for anastomosis in a

**Table 3** Rectal wall thickness before and after radiotherapy

Variable	RP group (n=23)	nRP group (n=26) <sup>a</sup>	P
Rectal wall thickness before radiotherapy (mm, $\bar{x} \pm s$ )	3.8±1.1	3.3±0.7	0.05
Rectal wall thickness after radiotherapy (mm, $\bar{x} \pm s$ )	6.4±1.5	3.5±0.6	<0.01
Relative change ( $\Delta L\%$ )	78.1±43.8	13.6±34.4	<0.01

<sup>a</sup>, rectal wall thickness before radiotherapy was not assessable in 3 patients due to the absence of raw data. RP, radiation proctitis; nRP, non-RP;  $\Delta L\%$ , the relative change of rectal wall thickness.



**Figure 4** Correlation analysis of  $\Delta Vp\%$  and  $\Delta L\%$ .  $\Delta Vp\%$ , the relative change of pelvic mesenteric adipose volume;  $\Delta L\%$ , the relative change of rectal wall thickness.

typical resection, is still within the irradiation field (19,30), and so the distal rectum is inevitably exposed to radiation injury. It was found that the use of a nonirradiated bowel for at least one end of an anastomosis substantially lowered the anastomotic leakage rate (31). Hence, we suggest that the scope of proximal bowel resection should be above the S1 level in radical operation for patients with RP.

CT or MRI has been used to examine the area of adipose tissues on a single cross-section passing through the umbilicus in order to evaluate the total abdominal adipose content and the visceral adipose content (32-35). However, for rectal cancer patients receiving radiotherapy, this method has failed in measuring the  $\Delta Vp\%$ . In this study, the reconstructed images were analyzed with the ANYTHINK GVCN system, through which we could continuously delineate the mesenteric area in any plane, and then calculate the total mesenteric adipose volume in the target area. This measurement has high reproducibility and provides a quantitative evaluation basis for comparing changes in abdominal and  $\Delta Vp\%$ .

Manifestations in typical images of RP can include the thickening of the rectal wall and the obvious thickening of the mucosa and/or serosal layer, which present a stratified change or “target sign” (36). In the previous study, T2 cross-sectional MRI images of the pelvis were used to measure

the maximum diameter of rectal wall thickness, excluding the tumor location, before and after radiotherapy (19). The data of rectal wall thickness were collected from the radiation enteritis database for analysis. Compared with the nRP group, the relative change of rectal wall thickness ( $\Delta L\%$ ) in the RP group was greater. The correlation analysis indicated that  $\Delta Vp\%$  was highly correlated with  $\Delta L\%$  in the RP group, but this was not the case for the nRP group. This confirms that  $\Delta Vp\%$  and  $\Delta L\%$  possess synergistic diagnostic values for RP.

The FOWARC study included 495 locally advanced rectal cancer patients who received neoadjuvant treatment and were randomly assigned to the mFolfox6 chemotherapy group, the fluorouracil + radiotherapy group, or the mFolfox6 + radiotherapy group. Study results revealed that the incidence of anastomotic leakage was 7.9%, 19.8%, and 18.1% respectively in the three groups, suggesting that preoperative neoadjuvant radiotherapy substantially increases the incidence of postoperative anastomotic leakage (8). In our study, anastomotic leakage occurred in 8 of 23 patients (34.8%) in the RP group and 4 of 29 patients (13.8%) in the nRP group. The incidence of anastomotic stenosis in the RP group was markedly higher than that in the nRP group (30.4% vs. 3.4%,  $P=0.02$ ), implying that RP was a risk factor for anastomotic leakage and stenosis.

There are also some limitations in this study. Firstly, this was a retrospective study, and the sample size was relatively small. Secondly, the mesenteric adipose volume was measured by manual sketching, which might have inherently led to random errors. The development of artificial intelligence and the application of the computer to sketch automatically will be conducive to reducing these inconsistencies.

## Conclusions

The  $\Delta Vp\%$  which correlated with the thickness of the rectal wall, demonstrated a satisfactory sensitivity and specificity

in diagnosing RP. Apply CT to quantitative measurement of the  $\Delta Vp\%$  is thus viable as a simple and noninvasive evaluation method.

## Acknowledgments

The authors would like to thank Rong Zhang for software support.

*Funding:* This work was supported by the Natural Science Foundation of Guangdong Province (No. 2018A030310319).

## Footnote

*Reporting Checklist:* The authors have completed the MDAR reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-5102>

*Data Sharing Statement:* Available at <http://dx.doi.org/10.21037/atm-20-5102>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-5102>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethical approval and patient informed consent are waived as we analyzed the CT images retrospectively, without any interventions or hazard to patients.

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**Cite this article as:** Cai Y, Ma T, Zhong Q, Qin Q, Cao W, Liu Z, Ke J, Wang H. Quantitative CT measurement of left colonic and pelvic mesenteric adipose volume in radiation proctitis. *Ann Transl Med* 2020;8(14):882. doi: 10.21037/atm-20-5102