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Comprehensive abdominal composition evaluation of rectal cancer patients with anastomotic leakage compared with body mass index-matched controls

Shao SL *et al*. Abdominal composition and anastomotic leakage

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Abstract

BACKGROUND

Anastomotic leakage (AL) is a fatal complication in patients with rectal cancer after undergoing anterior resection. However, the role of abdominal composition in the development of AL has not been studied.

AIM

To investigate the relationship between abdominal composition and AL in rectal cancer patients after undergoing anterior resection.

METHODS

A retrospective case-matched cohort study was conducted. Complete data for 78 patients with AL were acquired and this cohort was defined as the AL group. The controls were matched for the same sex and body mass index (± 1 kg/m^2). Parameters related to abdominal composition including visceral fat area (VFA), subcutaneous fat area (SFA), subcutaneous fat thickness (SFT), skeletal muscle area (SMA), skeletal muscle index (SMI), abdominal circumference (AC), anterior to posterior diameter of abdominal cavity (APD), and transverse diameter of abdominal cavity (TD) were evaluated base on computed tomography (CT) images based on the following Hounsfield Unit (HU) thresholds: SFA: -190 to -30, SMA: -29 to 150 and VFA: -150 to -20. The significance of abdominal composition-related parameters was

quantified using feature importance analysis; an artificial intelligence method used to evaluate the contribution of each included variable.

RESULTS

Two thousand two hundred and thirty-eight rectal cancer patients who underwent anterior resection from 2010 to 2020 in a large academic hospital were investigated. Finally, 156 cases were enrolled in the study. Patients in the AL group showed a longer operative time (225.03 ± 55.29 *vs* 207.17 ± 40.80, $P = 0.023$), exhibited lower levels of preoperative hemoglobin (123.32 ± 21.17 *vs* 132.60 ±1 6.31, $P = 0.003$) and albumin (38.34 ± 4.01 *vs* 40.52 ± 3.97, $P = 0.001$), larger tumor size (4.07 ± 1.36 *vs* 2.76 ± 1.28, $P < 0.001$) and later cancer staging ($P < 0.001$) compared to controls. Patients who developed AL exhibited a larger VFA (125.68 ± 73.59 *vs* 97.03 ± 57.66, $P = 0.008$) and a smaller APD (77.30 ± 23.23 *vs* 92.09 ± 26.40, $P < 0.001$) and TD (22.90 ± 2.23 *vs* 24.21 ± 2.90, $P = 0.002$) compared to their matched controls. Feature importance analysis revealed that TD, APD, and VFA were the three most important abdominal composition-related features.

CONCLUSION

AL patients have a higher visceral fat content and a narrower abdominal structure compared to matched controls.

Key Words: Anastomotic leakage; Abdominal composition; Rectal cancer; Body mass index-matched; Anterior to posterior diameter; Transverse diameter

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Core Tip: We investigated the association between abdominal composition and anastomotic leakage in rectal cancer patients who underwent anterior resection in a large academic hospital from 2010 to 2020. The data revealed that patients who developed anastomotic leakage had a higher visceral fat content and a narrower abdominal structure, despite body mass index matching.

INTRODUCTION

Compelling evidence demonstrates that total mesorectal resection (TME) successfully reduces the local recurrence rate of rectal cancer and is the gold standard for managing mid- and low-lying rectal cancer[1-3]. However, the morbidity of anastomotic leakage (AL), a worrisome complication of TME, is on the rise[4]. Once AL develops, it often requires reintervention and can lead to perioperative death and adverse oncology outcomes[5-7]. Early identification of patients at high risk of AL is critical to AL prevention, reduction of the reoperation rate, and will guide intraoperative decisions (for instance on whether to choose a diverting ileostomy or not), and improve perioperative management.

Numerous studies have explored the risk factors associated with AL in rectal cancer patients who underwent anterior resection[8,9]. However, there is no effective approach for predicting AL, implying that potential predictors should be explored. Recent studies show that some abdominal composition related factors are key contributors to AL in patients with colorectal cancer after undergoing surgery[10]. Theoretically, a less visceral fat content and a bigger abdominal volume are more favorable for surgeons to perform anterior resection procedure and thus leads to less technically difficult, shorter operation time and lower probability of AL[11]. Computed tomography (CT) images have been employed to assess the possible effects of abdominal composition related parameters, including visceral fat area (VFA) and skeletal muscle index (SMI), on patient surgical outcome[10,12-15]. Large VFA, for

instance, is potentially effective in predicting AL in patients with colorectal cancer who received anterior resection despite reports to the contrary[9]. Additionally, SMI, measured by a CT scan of the lower margin of the third lumbar spine, is a reliable indicator of the systemic nutritional status and is associated with perioperative complications[16]. Additional indicators, including abdominal circumference (AC), anterior to posterior diameter of abdominal cavity (APD), and transverse diameter of abdominal cavity (TD) are suggested to exert potential effects on perioperative complications but their roles in AL is unknown.

Considering the impact of abdominal composition on the surgeons and patients, it is hypothesized that the abdominal composition of rectal cancer patients who developed AL after anterior resection may be different from that of individuals with similar body mass index (BMI) and did not develop AL. Here, we compared the abdominal composition between AL patients and sex- and BMI-matched controls.

MATERIALS AND METHODS

Patients

A total of 2238 medical records of rectal cancer patients who underwent anterior resection in our center from January 1, 2010, to January 1, 2020, were reviewed. Of note, 173 patients were excluded due to non-primary rectal adenocarcinoma (n = 32) and missing clinical data (n = 141). All patients underwent a 90-d follow-up. Of the 2065 subjects, 107 (5.18%) developed clinical AL (*i.e.*, grade B and C). Among the AL patients, 29 patients were excluded for missing CT images; the remaining 78 patients were included in the final analysis and defined as the AL group. The control group was matched 1:1 for the same sex and BMI (± 1 kg/m^2) from patients who did not develop AL. A flowchart of this study is shown in Figure 1.

Definition and variables

In this study, rectal cancer is defined as a tumor located between the dentate line and sacral promontory. AL refers to clinical AL, including grade B and grade C, defined as disruption and defect in intestinal wall integrity at the anastomosis site, making the internal and external compartments communicate with each other[17]. The AL diagnosis is contingent on the fecal fluid from pelvic draining or water-soluble contrast agent enema and extra-rectal imaging. Alternatively, when AL was suspected, perianastomotic abscess or effusion detected by CT was examined to diagnose AL. Because water-soluble contrast agent enema is not performed routinely in our center, AL of grade A was not included. Clinical variables gender, age, height, weight, BMI, ASA score, previous abdominal history, hypertension, diabetes, cigarette smoking, alcohol use, tumorous obstruction, preoperative cleansing enema, preoperative antibiotic use, distance between tumor and anal margin, neoadjuvant, preoperative hemoglobin, preoperative albumin, type of operation, tumor size, clinical tumor stage, operation time, number of linear stapler firings, indwelling pelvic drainage tube, indwelling trans-anal tube, and stoma were also considered. Abdominal composition-related parameters: BMI, AC, subcutaneous fat area (SFA), subcutaneous fat thickness (SFT), skeletal muscle area (SMA), SMI, VFA, APD, and TD.

Assessment of abdominal composition associated parameters

Data of BMI and AC were acquired from medical records, whereas other indicators were examined at the lower margin of the third lumbar (L3) plane of the unenhanced CT image using Slice-O-Matic software (version 5.0; Tomovision, Montreal, Canada). CT images were saved in DICOM (Medical Digital Imaging and Communication) format and retrieved from the institutional database. SFA, SMA, and VFA were measured by setting Hounsfield Unit (HU) thresholds (SFA: -190 to -30, SMA: -29 to 150 and VFA: -150 to -20)[18]. SFT: The vertical distance from the linear alba to the skin; SMI: SMA/hight^2 (cm^2/m^2)[19,20]; APD: The vertical distance from the linear alba to

the anterior edge of the L3 spine; TD: Transverse diameter of the abdominal cavity through the anterior edge of the L3 spine.

Statistical analysis

Continuous variables were presented as average values (standard deviations SD), whereas categorical variables were presented as numerical values (percentages). Student's *t*-test and chi-square test were used to compare continuous variables and categorical variables, respectively. A P value of < 0.05 denoted statistical significance. All statistical analyses were performed in IBM SPSS 24.0 (SPSS for Windows, IBM Corporation, Armonk, NY, United States).

Feature importance analysis

Feature importance analysis is an artificial intelligence method used for examining the importance of each included feature. This approach is based on some ensemble learning algorithms, such as, random forest and XGboost. In this study, we used the random forest analysis to calculate the importance of each abdominal composition related parameter. Random forest is an ensemble classifier based on a combination of multiple decision trees which are generated through sampling from the original data set and the final predictions is voted by integrating all the trees. Mean decrease accuracy was calculated by randomly permuting a variable to reassess the predictions. If a variable is important, the mean decrease accuracy will show a large change. Therefore, the random forest algorithm could compute the importance of each included variable. This procedure was conducted using Scikit-learn package (version 0.24.1) in Python 3.8.5.

RESULTS

Demographic and clinical characteristics

A total of 156 patients were included in the final analysis. Table 1 shows the comparison of the clinical characteristics between the AL group and the control group. Compared to the controls, the patients in the AL group underwent a longer operative time (225.03 ± 55.29 *vs* 207.17 ± 40.80, $P = 0.023$). Patients in the AL group exhibited lower levels of preoperative hemoglobin (123.32 *vs* 132.60, $P = 0.003$) and albumin (38.34 *vs* 40.52, $P = 0.001$), larger tumor size (4.07 *vs* 2.76, $P < 0.001$), and later cancer staging ($P < 0.001$) compared to controls. The ASA score had a marginal effect ($P = 0.049$). No statistical difference was found between the AL group and the control group for other features.

Comparison of abdominal composition related parameters

Table 2 shows the difference in abdominal composition related parameters between the AL group and the control group. Analysis revealed that patients in the AL group had a larger VFA (125.68 *vs* 97.03, $P = 0.008$), a smaller APD (77.30 *vs* 92.09, $P < 0.001$), and a smaller TD (22.90 *vs* 24.21, $P = 0.002$) compared to those in the control group. These results are intriguing and suggest a potential contribution of a narrower abdominal cavity to AL development. Differences in other indicators were not statistically significant. A radar plot demonstrated the comparison of these indicators between the AL group and the control group (Figure 2).

Feature importance analysis

Although determination of statistical significance of abdominal composition-related indicators can be used to prove correlations, it is not sufficient. Feature importance analysis was conducted to quantify the contribution of each abdominal composition related indicator in AL development. Results demonstrated that TD, APD, and VFA are the three most important features (Figure 3). Additionally, we performed univariate and multivariate logistic regression analysis to investigate whether the VFA, APD, and TD were

independent risk factors for AL. The data indicated that the VFA, APD, and TD were independent risk factors ($P < 0.05$) (Supplementary Table 1).

DISCUSSION

The mechanism underlying AL occurrence involves several factors. The present work compared the clinical characteristics and abdominal composition in rectal cancer patients who received anterior resection and developed AL to controls who were matched for sex and BMI. This study was conducted in a large academic hospital in which more than 4000 gastrointestinal operations were performed annually. Analysis revealed a 5.18% incidence of clinical AL, which concur with previous reports[21-23]. In this study cohort, when comparison was conducted in clinical characteristics, a lower level of preoperative hemoglobin and albumin, a longer operative time, a larger tumor size, and a later cancer stage were associated with AL. In addition, when comparing abdominal composition related parameters, it is interesting to find that a higher visceral fat content and a narrower abdominal structure are associated with AL. This work provides concrete evidence that the occurrence of AL is not only associated with patient related factors, but also the underlying factors that may affect surgical technique.

Related studies have demonstrated that BMI, an easily available and most commonly used index of obesity, is a risk factor of AL in rectal cancer patients who received anterior resection. However, other studies have reported contrary reports[24,25]. Considering BMI cannot distinguish between the content and distribution of fat and skeletal muscle, it is imperative to explore whether fat and skeletal muscle content or distribution potentially impact the development of Verduin *et al*[9] investigated the role of VFA on AL in 2370 colon cancer patients and the results implicated VFA as an independent risk factor of AL in the elective colon resection patients (OR = 1.026, $P = 0.035$). Elsewhere, a study employed CT images to quantify the fat distribution and proposed the association of high adipose tissue with higher risk AL in rectal

cancer patients[26]. However, whether VFA and other abdominal composition potentially influences the occurrence of AL in patients with a similar BMI remains to be further evaluated. In addition, owing to the narrow pelvic structure, the male sex is widely accepted as an independent risk factor for AL in rectal cancer patients who received anterior resection, and some evidence has demonstrated the role of pelvic related parameters on AL[27]. Theoretically, a narrow pelvic structure is associated with the increased difficulty of the operation and prolonged operation time. All these features may increase the risk of AL. However, whether a narrow abdominal structure plays a similar role in AL occurrence is not known.

By comparing the differences in abdominal composition between AL and non-AL patients through sex and BMI matching, we found a higher VFA (125.68 *vs* 97.03, $P = 0.008$) and smaller narrow abdominal cavity structure (APD, 77.30 *vs* 92.09, $P < 0.001$; TD, 22.90 *vs* 24.21, $P = 0.002$) in AL patients than that of the controls. The difference in skeletal muscle-related parameters, including SMA and SMI, were not significant, which may be ascribed to the unbalanced matching of other variables between the AL patients and controls, because various variables are associated with muscle content and density. This study provides support to the hypothesis that even with similar BMI, AL patients are characterized by a higher VFA and a narrower abdominal structure.

This study has several limitations. First, as a single-center case-matched study, selection bias cannot be completely ignored. Second, although a standard and strict screening and matching criteria were employed, the large initial sample size and the small sample size for analysis may imply that the research results needed be further validated on a larger cohort. Third, some variables impacting abdominal composition were not collected, including whether subjects are athletes, metabolic syndrome, *etc.* Lastly, this study was performed based on abdominal CT images, as such; some indicators such as muscle density and intermuscular fat could not be evaluated in detail. Given

the retrospective nature of this study and the small sample size, future longitudinal investigations with large samples are advocated to provide reliable data to determine causality for the correlation of abdominal components and AL.

CONCLUSION

The present analysis demonstrates the difference in abdominal components between AL patients and controls matched for sex and BMI. The contribution of each indicator to the development of AL was demonstrated. Intriguingly, in addition to the differences in VFA, the negative effects of APD and TD on AL were observed. This study adds considerable value to the field of AL preoperative risk assessment in rectal cancer patients. VFA, APD, and TD are potential indicators for predicting the risk of AL and can guide surgical decision-making (for example, performing a temporary ileostomy for high-risk patients).

ARTICLE HIGHLIGHTS

Research background

Compelling evidence demonstrates the relationship of abdominal composition and postoperative complications. Anastomotic leakage (AL) is a fatal complication in patients with rectal cancer who have received anterior resection. However, the roles of abdominal composition on AL have not been studied.

Research motivation

To study the characteristics of abdominal components in patients who received rectal cancer surgery and developed AL.

Research objectives

To add risk factors of AL prediction in rectal cancer patients undergoing anterior resection for guiding surgical decision-making, such as, performing a temporary ileostomy or not.

Research methods

A retrospective case-matched cohort study was conduct. The abdominal composition was quantified base on computed tomography images by setting Hounsfield Unit thresholds. The abdominal composition related parameters were compared and the importance of these indicators was quantified using feature importance analysis.

Research results

A total of 156 cases were included in this study. Comparing the abdominal composition related parameters demonstrated that patients who developed AL exhibited a larger visceral fat area (VFA, 125.68 ± 73.59 *vs* 97.03 ± 57.66, $P = 0.008$) and a smaller anterior to posterior diameter of abdominal cavity (APD, 77.30 ± 23.23 *vs* 92.09 ± 26.40, $P < 0.001$) and transverse diameter of abdominal cavity (TD, 22.90 ± 2.23 *vs* 24.21 ± 2.90, $P = 0.002$). Feature importance analysis revealed TD, APD, and VFA to be the three most important abdominal composition related parameters.

Research conclusions

Rectal cancer patients who had a higher visceral fat content and a narrower abdominal structure might be at a higher risk of developing AL.

Research perspectives

A narrow abdominal structure is associated with the increased difficulty of the operation and prolonged operation time. In addition, the association of abdominal composition related parameters and postoperative complications

were reported. But, whether abdominal composition is associated with AL is not known.

Figure Legends

Figure 1 Flow chart of patient inclusion and exclusion.

Figure 2 Radar plot for the comparison of abdominal composition related parameters between the anastomotic leakage group and the Control group. AC: Abdominal circumference; SFA: Subcutaneous fat area; SFT: Subcutaneous fat thickness; SMA: Skeletal muscle area; SMI: Skeletal muscle index (SMA/height^2); VFA: Visceral fat area; APD: Anterior to posterior diameter of abdominal cavity; TD: Transvers diameter of abdominal cavity; AL: Anastomotic leakage.

Figure 3 Importance of each feature in the development of anastomotic leakage. AC: Abdominal circumference; SFA: Subcutaneous fat area; SFT: Subcutaneous fat thickness; SMA: Skeletal muscle area; SMI: Skeletal muscle index (SMA/height^2); VFA: Visceral fat area; APD: Anterior to posterior diameter of abdominal cavity; TD: Transvers diameter of abdominal cavity; AL: Anastomotic leakage.

Table 1 Comparison of demographic and clinicopathologic characteristics in patients with anastomotic leakage and controls groups

Variables	Controls (n = 78)	AL (n = 78)	P value
Male sex, n (%)	57 (71.3)	57 (71.3)	1.000
Age, mean (SD), yr	58.23 (9.46)	56.82 (10.54)	0.380
Height, mean (SD), cm	166.23 (7.92)	166.87 (7.34)	0.601
Weight, mean (SD), kg	63.41 (11.62)	65.40 (11.39)	0.282
Operative time, mean (SD), min	207.17 (40.80)	225.03 (55.29)	0.023
Laparoscopic surgery, n (%)	77 (98.7)	76 (97.4)	1.000
Location of tumor, mean (SD), cm	7.86 (3.39)	8.22 (3.59)	0.507
Intraperitoneal chemotherapy, n (%)	50 (64.1)	54 (69.2)	0.497
Cleansing enema, n (%)	57 (73.1)	60 (76.9)	0.579
Indwelling trans-anal tube, n (%)	73 (93.6)	68 (87.2)	0.174
Indwelling drainage tube, n (%)	72 (92.3)	74 (94.9)	0.746
Tumorous obstruction, n (%)	1 (1.3)	6 (7.7)	0.053
Cigarette smoking, n (%)	24 (30.8)	35 (44.9)	0.098
Alcohol use, n (%)	14 (17.9)	21 (26.9)	0.249
Hypertension, n (%)	20 (25.6)	19 (24.4)	1.000
Diabetes, n (%)	10 (12.8)	11 (14.1)	1.000
Previous abdominal surgery, n (%)	11 (14.1)	5 (6.4)	0.186
Preoperative antibiotics, n (%)	75 (76.2)	72 (92.3)	0.303
Hemoglobin, mean (SD), g/L	132.60 (16.31)	123.32 (21.17)	0.003
Albumin, mean (SD), g/L	40.52 (3.97)	38.34 (4.01)	0.001
Neoadjuvant, n (%)	1 (1.3)	3 (3.8)	0.620
Tumor size, mean (SD), cm	2.76 (1.28)	4.07 (1.36)	< 0.001
ASA, n (%)			0.049
1	17 (21.86)	9 (11.5)	
2	56 (71.8)	56 (71.8)	
3	5 (6.4)	13 (16.7)	
Stages, n (%)			< 0.001

1	67 (85.9)	19 (24.4)	
2	5 (6.4)	33 (42.3)	
3	6 (7.7)	26 (33.3)	
Number of linear stapler firings, *n* (%)			0.393
1	38(48.7)	37 (47.4)	
2	39 (50.0)	37 (47.4)	
3	1 (1.3)	4 (5.1)	
Stoma, *n* (%)	20 (25.6)	18 (23.1)	0.852

SD: Standard deviation; ASA: American society of Anesthesiologists score; AL: Anastomotic leakage.

Table 2 Comparison of abdominal parameters in patients with anastomotic leakage and controls groups

Variables	Controls (*n* = 78)	AL (*n* = 78)	*P* value
BMI (SD), kg/m^2	23.05 (3.05)	23.17 (2.88)	0.797
AC, mean (SD), cm	87.00 (10.94)	89.71 (14.20)	0.120
SFA, mean (SD), cm^2	108.72 (54.12)	113.72 (55.87)	0.571
SFT, mean (SD), mm	18.68 (8.20)	18.03 (7.31)	0.601
SMA, mean (SD), cm^2	127.89 (29.57)	132.06 (33.40)	0.410
SMI, mean (SD), cm^2/m^2	46.00 (8.81)	47.10 (10.57)	0.482
VFA, mean (SD), cm^2	97.03 (57.66)	125.68 (73.59)	0.008
APD, mean (SD), mm	92.09 (26.40)	77.30 (23.23)	< 0.001
TD, mean (SD), cm	24.21 (2.90)	22.90 (2.23)	0.002

BMI: Body mass index; SD: Standard deviation; AC: Abdominal circumference; SFA: Subcutaneous fat area; SFT: Subcutaneous fat thickness; SMA: Skeletal muscle area; SMI: Skeletal muscle index (SMA/height^2); VFA: Visceral fat area; APD: Anterior to posterior diameter of abdominal cavity; TD: Transvers diameter of abdominal cavity; AL: Anastomotic leakage.

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