생체 전기 임피던스 분석으로 측정된 내장 지방 단면적이 대장 수술의 임상병리학적 결과에 미치는 영향

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Impact of Visceral Fat Area Measured by Bioelectrical Impedance Analysis on Clinico-Pathologic Outcomes of Colorectal Surgery

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Purpose: This study investigated the relationship between the visceral fat area (VFA) and clinico-pathological outcomes in patients with colorectal cancer (CRC).

Methods: This retrospective study included 204 patients who underwent anthropometric measurement by bioelectrical impedance analysis (BIA) before surgical treatment for CRC between January 2016 and June 2020.

Results: According to the average value of the visceral fat area, 119 (58.3%) patients had a low visceral fat area, and 85 (59.1%) patients had a high visceral fat area. Patients with visceral obesity showed a higher BMI compared to patients without visceral obesity, (21.8 ± 1.9 vs. 25.7 ± 2.5 , $P < 0.001$). There was no significant difference in the overall perioperative outcomes including total operation time, time to gas out, sips of water, soft diet, hospital stay, and morbidity between patients in the low and high VFA groups. We divided patients into two subgroups according to the degree of cancer progression and more advanced cases with low VFA showed significantly more total and positive retrieved lymph nodes (LNs) (20.9 ± 10.3 vs. 16.1 ± 7.1 , $P = 0.021$ and 3.3 ± 2.9 vs. 2.2 ± 2.3 , $P = 0.019$, respectively) and a higher proportion of more than 12 retrieved LNs compared to patients with a high VFA (95.1% vs. 90.0%, $P = 0.047$). Body composition analysis showed that phase angle, muscle composition, and body fluid composition were not statistically different between the two groups. However, body fat mass was statistically higher in the high VFA group (22.0 ± 4.6 vs. 12.8 ± 3.1 , $P < 0.001$).

Conclusion: Visceral obesity measured by BIA showed lower total and positive retrieved LNs and was not associated with adverse peri-operative outcomes, inflammatory and nutritional, and pathologic outcomes for CRC.

Key Words: Colorectal neoplasm, Nutrition assessment, Body composition, Electric impedance, Prognosis

Received June 24, 2021; Accepted June 26, 2021

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Conflict of interest: None.

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INTRODUCTION

Colorectal cancer (CRC) is the third most frequently diagnosed cancer and second most mortality in worldwide. Obesity is a global health growing problem. According to World Health Organization, 39% of adults aged 18 years and over were overweight, and 13% of adults were obese. The re-

relationship between body weight and several cancers is now well recognized obesity is now a well-established risk factor for development of CRC and is also associated with increased mortality from CRC.¹⁻³ In clinical setting, body mass index has been used to one of the most reliable anthropometric methods to check obesity, however it doesn't reflect the accumulation of adipose tissue, especially intra-abdominal or visceral fat tissue.^{4,5}

Some studies showed that increase of visceral fat was associated with post-operatively clinical outcomes and oncologic outcomes. A systemic review demonstrated that visceral obesity, especially, is associated with an increased risk of longer hospital stay, higher morbidity, and longer operative time after colon surgery and that obese patients had lower chances of survival and more aggressive biological tumor features.⁶ However, a study reported that patients with visceral obesity tended to have significantly better overall survival than patients with non-visceral obesity and controversies exist regarding the correlation between visceral obesity and the outcome of colon cancer.

Bioelectrical impedance analysis (BIA) is a non-invasive technique that requires a low cost equipment available at many health care services for routine nutritional assessment describes the percentages of fat, protein, minerals in human bodies. Recently, several studies have established a relationship between some parameters of body composition such as skeletal muscle mass index, the index of sarcopenia or phase angle and clinical and oncologic outcomes of CRC.⁷⁻⁹ However, to our knowledge, there were no studies about using BIA to find the effects of visceral fat on outcomes of CRC. Therefore, our study aimed to compare the effects of visceral obesity measuring by bioelectrical impedance analysis using Inbody 770 (Biospace, Seoul, Korea) on clinical and pathologic outcomes to patients who was treated with surgery for CRC.

MATERIALS AND METHODS

1. Patients and data collection

The study group included 204 patients who underwent laparoscopic surgery for colorectal adenocarcinoma between January 2016 and June 2020. The patients were divided into

low and high groups according to visceral fat area (VFA) measured by BIA. The exclusion criteria included synchronous or previous malignancies, malignancies other than adenocarcinoma, and familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer. This study protocol was approved by the Institutional Review Board of the Dongsan Medical Center, and informed consent was obtained from all patients.

Data on patient demographics, including age, sex, pre-operative carcinoembryonic antigen, body mass index (BMI), and location of the tumor, platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR) and platelet-neutrophil index (PNI) were collected retrospectively. Perioperative outcomes included operation time, time to gas out, sips of water, and soft diet, hospital stay, morbidity within 30 days and Clavien-Dindo classification. Pathologic outcomes included tumor, node, metastasis (TNM) stage, histology, number of harvested lymph nodes and positive lymph nodes, metastatic lymph node ratio, tumor size, lymphovascular invasion, perineural invasion, and extranodal tumor deposits.

2. Bioimpedance analysis

BIA was performed using Inbody 770 (Biospace) to estimate patient's body composition at their first visit. Among various parameters of BIA, we categorized variables as body composition and metabolic index, fat index, muscle index, obesity index, and phase angle. We used the average value of the VFA as the cut-off level, because there have been no previous studies on the cut-off value for VFA using BIA. Skeletal muscle index (SMI) was calculated using Baumgartner's definition ($\text{appendicular skeletal muscle mass/height}^2$).

3. Preoperative evaluation and surgical treatment

All of the patients underwent preoperative evaluation including colonoscopy, computed tomography scan of chest and abdomen, and magnetic resonance imaging of the pelvis. Some patients underwent positron emission tomography scans for check distant metastasis. We followed the general principles of complete mesocolic or mesorectal excision and central vascular ligation for CRC. The primary tumor was resected by sharp dissection of the visceral plane from the parietal fascia layer along with the entire regional mesocolon in

an intact package. For right-sided colon cancer, radical lymphadenectomy including D2 or D3 dissection along the primary feeding vessels along a vertical line to expose the superior mesenteric vein was performed. For left-sided colon or rectal cancer, high ligation or selectively low ligation of the inferior mesenteric artery with lymph node dissection according to the tumor location was performed. Tumor stages were classified in accordance with the American Joint Committee on Cancer 8th Edition staging system.

4. Statistical analysis

The results are presented as medians with ranges for continuous outcomes and as frequencies with percentages for categorical outcomes. Categorical variables were analyzed using chi-square and Fisher's exact tests. Continuous variables were analyzed with independent t-test and Mann-Whitney test. A P-value <0.05 was considered to indicate statistical significance. The statistical analyses were performed with IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA).

Table 1. Patient characteristics

Variables	Low VFA (n=119)	High VFA (n=85)	P-value
Age (y)	66.4±9.9	65.5±10.1	0.544
Sex			0.053
Male	88 (73.9)	52 (61.2)	
Female	31 (26.1)	33 (38.8)	
Preoperative CEA (ng/mL)	8.0±23.2	3.4±4.8	0.073
Preoperative CRP	0.74±1.6	0.35±0.5	0.060
ASA score			0.872
I	34 (28.6)	25 (29.4)	
II	68 (57.1)	50 (58.8)	
III	17 (14.3)	10 (11.8)	
BMI (kg/m ²)	21.8±1.9	25.7±2.5	<0.001
Location of tumor			0.256
Right-sided	32 (26.9)	17 (20.0)	
Left-sided	87 (73.1)	68 (80.0)	
PLR	181.7±110.7	190.7±102.9	0.548
NLR	3.3±3.4	3.1±2.6	0.700
PNI	67.0±27.0	72.6±32.6	0.199

Values are presented as mean±standard deviation or number (%). VFA = visceral fat area; CEA = carcinoembryonic antigen; CRP = C-reactive protein; ASA = American Society of Anesthesiologists; BMI = body mass index; PLR = platelet-to-lymphocyte ratio; NLR = neutrophil to lymphocyte ratio; PNI = prognostic nutritional index.

RESULTS

1. Patient characteristic

According to the average value of VFA, 119 (58.3%) patients had low VFA and 85 (59.1%) patients had high VFA. Patients' characteristics which were divided into amount of visceral fat are summarized in Table 1. Preoperative carcinoembryonic antigen and C-reactive protein tended to higher in non-visceral obesity (8.0±23.2 vs. 3.4±4.8, P=0.073 and 0.74±1.6 vs. 0.35±0.5, P=0.060, respectively). Patients with high VFA showed significantly higher BMI than patients with low VFA (21.8±1.9 vs. 25.7±2.5, P<0.001). All inflammation indexes including PLR, NLR, PNI had no statistical differences between two groups.

2. Perioperatively clinical outcomes

Table 2 showed no significant difference in the overall perioperative outcomes including total operation time, time to gas out, sips of water, soft diet, and hospital stay between patients with low and high VFA groups. Also, there were no significant difference in morbidity within 30 days after surgery, the proportion of Clavien-Dindo classification >3a, and neo-adjuvant chemotherapy.

3. Postoperatively pathologic outcomes

Comparing to non-visceral obesity, there were no significant difference in overall TNM stage, differentiation, the number of total lymph node harvested and pathologically

Table 2. Perioperative clinical outcomes

Variables	Low VFA (n=119)	High VFA (n=85)	P-value
Operation time (min)	204.5±101.0	208.6±93.1	0.762
Time to gas out (d)	3.1±2.2	2.9±1.6	0.293
Time to sips of water (d)	4.1±3.4	3.9±5.0	0.687
Time to soft diet (d)	6.5±3.8	6.3±5.1	0.805
Length of stay (d)	10.8±6.5	9.6±0.9	0.188
Morbidity within 30 days after surgery	41 (34.4)	27 (31.8)	0.688
Clavien-Dindo classifications >3a	25 (21.0)	17 (20.0)	0.861
Neoadjuvant chemotherapy	27 (22.7)	18 (21.2)	0.797

Values are presented as mean±standard deviation or number (%). VFA = visceral fat area.

Table 3. Postoperative pathologic outcomes

Pathologic outcomes	All patients			Stage 1 and 2			Stage 3 and 4		
	Low VFA (n=119)	High VFA (n=85)	P-value	Low VFA (n=78)	High VFA (n=55)	P-value	Low VFA (n=41)	High VFA (n=30)	P-value
Tumor stage			0.369			0.701			0.056
T1	27 (22.7)	25 (29.4)		24 (30.8)	20 (36.4)		1 (2.4)	5 (16.7)	
T2	21 (17.6)	18 (21.2)		19 (24.4)	14 (25.5)		4 (9.8)	4 (13.3)	
T3	60 (50.4)	39 (45.9)		35 (44.9)	21 (38.2)		26 (63.4)	19 (63.3)	
T4	11 (9.2)	3 (3.5)		0 (0.0)	0 (0.0)		10 (24.4)	2 (6.7)	
Nodal stage			0.417						0.140
N0	79 (66.4)	54 (63.5)					0 (0.0)	0 (0.0)	
N1	23 (19.3)	20 (23.5)					25 (61.0)	24 (80)	
N2	17 (14.3)	11 (12.9)					16 (39.0)	6 (20)	
Nodal status									
Negative	79 (66.4)	54 (63.5)	0.673				0 (0.0)	0 (0)	0.389
Positive	40 (33.6)	31 (36.5)					41 (88.0)	30 (100)	
Metastasis 1	5 (4.2)	4 (4.7)	0.363				5 (12.0)	3 (10.0)	0.773
Stage									
I, II	78 (65.5)	55 (64.7)	0.901						
III, IV	41 (34.5)	30 (35.3)							
Histology			0.061			0.050			0.656
Well differentiated	12 (9.2)	4 (2.4)		11 (14.1)	2 (3.6)		1 (2.4)	2 (6.7)	
Moderately differentiated	98 (82.4)	78 (91.8)		62 (79.5)	52 (94.5)		36 (87.8)	26 (86.7)	
Poorly differentiated	9 (7.6)	3 (3.5)		5 (6.4)	1 (1.8)		4 (9.8)	2 (6.7)	
Retrieved LNs	19.7±9.6	17.2±8.7	0.064	19.0±9.2	17.9±9.4	0.654	20.9±10.3	16.1±7.1	0.021
Retrieved LNs			0.074			0.394			0.047
≥ 12	107 (89.9)	69 (81.2)		68 (87.2)	45 (81.8)		39 (95.1)	24 (90.0)	
< 12	12 (10.1)	16 (18.5)		10 (12.8)	10 (18.2)		2 (4.9)	6 (10.0)	
Positive LNs	1.1±2.3	0.8±1.7	0.233				3.3±2.9	2.2±2.3	0.019
Tumor size (cm)	3.8±2.1	3.4±2.2	0.174	3.4±2.2	3.1±2.1	0.324	4.4±1.7	3.9±2.4	0.288
Lymphovascular invasion	40 (33.6)	14 (16.5)	0.008	19 (24.4)	3 (5.5)	0.005	21 (51.2)	11 (36.7)	0.223
MLR (%)	6.2±11.9	5.0±9.8	0.441				17.6±14.4	14.1±12.0	0.268
Perineural invasion	25 (21.0)	16 (18.8)	0.746	2 (2.6)	4 (7.3)	0.183	23 (56.1)	12 (40)	0.180
Extranodal tumor deposit	24 (40.7)	13 (36.1)	0.389				24 (64.9)	13 (52.0)	0.311

Values are presented as mean±standard deviation or number (%).

VFA = visceral fat area; LN = lymph node; MLR = metastatic lymph nodes ratio.

positive lymph node, tumor size, lymphovascular invasion, perineural invasion, and extranodal tumor deposit between two groups, except there were more lymphovascular invasion in patients with low VFA (33.6% vs. 16.5%, $P=0.008$) (Table 3).

To investigate the impact of VFA in nodal disease, we divided into two subgroups including stage one and two CRC and stage three and four CRC. In earlier CRC, there were no significant difference in tumor stage and patients with low VFA showed more poorly differentiated tumor histology (6.4% vs. 1.8%, $P=0.050$). The mean number of total and positive retrieved lymph nodes, the proportion of more than 12 lymph nodes harvested, and perineural invasion were not

significantly different, however low VFA group had more lymphovascular invasion than high VFA group (24.4% vs. 5.5%, $P=0.005$).

In more advanced CRC, patients with low VFA showed significantly more total and positive retrieved lymph nodes (20.9±10.3 vs. 16.1±7.1, $P=0.021$ and 3.3±2.9 vs. 2.2±2.3, $P=0.019$, respectively) and higher proportion of more than 12 retrieved lymph nodes compared to patients with high VFA (95.1% vs. 90.0%, $P=0.047$). Tumor sizes, lymphovascular invasion, metastatic lymph nodes ratio, perineural invasion, and extranodal tumor deposits were not significantly different between two groups.

Table 4. Inbody 770 body composition analysis of patients

Body analysis	Low VFA (n=119)	High VFA (n=85)	P-value
Height (cm)	162.3±8.8	162.4±9.6	0.969
Weight (kg)	57.8±8.6	68.1±11.3	<0.001
Phase angle (°)	5.1±0.7	5.0±0.7	0.658
Skeletal muscle mass (kg)	24.5±4.7	25.2±5.6	0.363
ASM (kg)	18.5±3.8	19.1±4.1	0.266
Skeletal muscle index (kg/m ²)	7.0±1.1	7.2±1.0	0.156
Body fluid (%)	33.2±5.7	68.1±6.8	0.352
ICF (%)	20.3±3.6	20.8±4.3	0.368
ECF (%)	12.9±2.1	13.2±2.6	0.329
Body fat mass (kg)	12.8±3.1	22.0±4.6	<0.001

Values are presented as mean±standard deviation.

VFA = visceral fat area; ASM = appendicular skeletal muscle mass; ICF = intracellular fluid; ECF = extracellular fluid.

4. Inbody 770 body composition analysis of patients

Table 4 showed the body composition analysis of patients between non-visceral obesity and visceral obesity patients using Inbody 770. Patients with high VFA had higher weight compared to patients with low VFA. Phase angle, muscle compositions including skeletal muscle mass, appendiceal skeletal muscle mass and SMI were not statistically different between two groups. Body fluid, intracellular fluid composition, and extracellular fluid composition showed no significant differences between two groups, however body fat mass was statistically higher in high VFA group (22.0±4.6 vs. 12.8±3.1, $P < 0.001$).

DISCUSSION

In this study, we investigated the surgical outcomes and short-term oncologic outcomes for visceraally obese patients with CRC. To our knowledge, this study is the first report to evaluate the effects of visceral obesity on CRC using BIA. The present study shows that among CRC patients, VFA measured by BIA was not associated with peri-operative outcomes, inflammatory and nutritional, and pathologic outcomes after colorectal surgery. However, patients with low VFA showed more total and positive retrieved lymph nodes and the proportion of more than 12 retrieved lymph nodes compared to patients with high VFA.

Traditionally, body fat composition The WHO BMI definition of obesity $\geq 30 \text{ kg/m}^2$ was adopted, but we also in-

cluded studies in which BMI was defined as $\geq 25 \text{ kg/m}^2$ for Asian populations. Visceral fat tissue has been acknowledged to be more pathogenic than BMI and visceral adipose tissue could be quantified by computerized tomography, and has been identified as a risk factor for colon cancer.^{10,11} Compared to subcutaneous adipose tissue, visceral revealed high levels of markers of inflammatory lipid metabolism and some of them associated with cancer stage.¹⁰ Gao et al.¹² reported that VFA measured by BIA showed satisfactory reliability with that measured by CT and suggested specific cut-off value for VFA by BIA in diagnosing visceral obesity for patients with gastric cancer in the Chinese population. Our study showed positive relationships between BMI and body fat mass and visceral fat have positive relationships. We think that VFA measured by BIA can be an index as surrogates of visceral obesity, although we could not compare the accuracy of BIA in estimating VFA with other index such as BMI, waist circumference, waist-to-hip ratio, or VFA measured by CT scan.

Some studies showed that obese patients have a significant risk of overall postoperative complications, surgical site infection, anastomotic leakage and colostomy complications. Kang et al.¹³ divided into the obese group and the non-obese group who underwent laparoscopic surgery for rectal cancer according to BMI and VFA measured by abdominal CT and demonstrated that VFA was more reliable predictive indicator than BMI in estimating early surgical outcomes for patients who underwent rectal cancer surgery. Yu et al.¹⁴ investigated VFA and general obesity and to compare visceral and general obesity as predictors of surgical outcomes of a CRC resection and described that there was no differences in morbidity, mortality, postoperative bowel recovery, and re-admission rate after surgery between the visceral obesity and visceral non-obesity groups. In the current study, visceral obesity has no influence on intraoperative difficulties, postoperative complications, and postoperative recovery in patients with CRC. Prospective studies with more sample-size are needed.

Some studies evaluated the importance of lymph node metastasis in colon cancer and found that visceral obesity was associated with a lower likelihood of metastatic lymph node involvement.^{15,16} Park et al.¹⁷ showed that a larger num-

ber of lymph nodes removed in patients without obesity than in patients with BMI=25.0~29.9 kg/m², but no differences compared with patients with higher BMI (>30.0 kg/m²). A study that evaluated the impact of visceral obesity on lymph node metastasis and overall survival in colon cancer reported that metastatic lymph node ratio was significantly associated only with lower VFA to total fat area ratio.¹⁸ Meanwhile, current guidelines for CRC treatment suggest that a minimum 12 lymph nodes need to be examined to establish nodal stage. Those guidelines recommend that less than 12 lymph nodes retrieved constitute the high-risk factors for recurrence and adjuvant chemotherapy is beneficial to those patients. In our study, non-visceral obesity patients showed more total and pathological lymph nodes harvested than patients with visceral obesity. We think that surgeon may have more difficulty to perform a radical lymphadenectomy in the excess fat tissue around major vessels in patients with visceral obesity. And identification of lymph nodes were difficult for pathologists.¹⁹

A recent study showed that sarcopenia had negatively impact on overall survival, disease-free survival, recurrence-free survival, and cancer-specific survival in patients with non-metastatic and metastatic CRC.²⁰ Phase angle that is defined as the ratio of resistance (intracellular and extracellular resistance) to reactance (cell membrane-specific resistance) expressed as an angle and is considered an indicator of cell membrane function. There were few studies about relation phase angle and other gastrointestinal cancers that low phase angle showed bad clinical and pathological outcomes.^{21,22} We tried to find the association between VFO and other nutritional index measured by BIA such as SMI and phase angle, however there was no statistical relationship between visceral obesity and those parameters.

Some previous studies reported the PLR are associated with fat respectively. Bahadır et al.²³ reported that lymphocyte count significantly was higher while increasing BMI and Samocha-Bonet et al.²⁴ found that platelet count had positive relation to BMI only in females. Because female had high body fat mass and excessive adipose tissue was shown to induce systemic and chronic inflammation through the release of inflammatory cytokines including interleukin-6 (IL-6). Yudkin et al.²⁵ have demonstrated an association between

obesity and IL-6 levels. IL-6 is inflammatory cytokines that plays a crucial role in increasing platelet count. However, inflammation factors including PLR, PNI, NLR showed no remarkable differences in non-visceral obesity patients to visceral obesity patients in this study.

The limitations of this study include its retrospective design, which is subject to incomplete data and potential selection bias in single institution. Secondly, our study included only small number of patients and didn't include survival data. Thirdly, the cut-off value of visceral obesity was the average value of the patients included in our study. Further prospective study with receiver operating characteristic curve to determine the cut-off value of visceral obesity measured by BIA is needed. In conclusion, visceral obesity measured by BIA showed lower total and positive retrieved lymph nodes and was no associated with peri-operative outcomes, inflammatory and nutritional, and pathologic outcomes for CRC.

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