Master's Thesis

Impact of Visceral Fat Area Measured by Bioelectrical Impedance Analysis on Clinicopathologic and Oncologic Outcomes of Colorectal Cancer

Department of Medicine

Graduate School of Keimyung University

Kyeong Eui Kim

Kyeong Eui Kim

Supervised by Sung Uk Bae

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Graduate School of Keimyung University

Kyeong Eui Kim

This master's thesis of Kyeong Eui Kim has been examined and approved by the thesis committee.

Committee Chair 정 운 경

Committee Member 배 성 욱

Committee Member 손 영 길

Graduate School of Keimyung University

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1. Introduction

Colorectal cancer is the third most frequently diagnosed cancer and second most mortality in worldwide (1,2). According to World Health Organization, 39% of adults aged 18 years and over were overweight, and 13% of adults were obese (3). The relationship between body weight and several cancers is now well recognized and obesity is now a well-established risk factor for development of CRC and is associated with increased mortality from CRC (4-6). The underlying mechanisms correlated obesity with CRC were not completely elucidated, but sustained inflammatory signaling, chronic insulin resistance, dysregulated adipokine induced by adipose tissue macrophage, and hypoxic and angiogenic environment of obese adipose tissue with elevated circulating cytokines are proposed as important factors for carcinogenesis (7).

Body mass index (BMI) has been used to one of the most reliable anthropometric methods to check obesity (8-10), but it doesn't reflect on the accumulation of adipose tissue, especially intra-abdominal or visceral fat tissue (11,12). Controversies exist regarding the correlation between visceral obesity and the outcome of colon cancer. Some studies showed that visceral obesity is associated with a poorer

clinical and oncologic outcomes including longer hospital stay, higher morbidity within 30 days, and longer operation time, more aggressive pathologic tumor features, and poorer survival rates (13,14). However, other studies reported that patients with visceral obesity tended to show protective effects on overall survival compared to patients with non-visceral obesity (15,16).

Body composition analysis describes the percentages of fat, protein, minerals in human bodies. Bioelectrical impedance analysis (BIA) is a non-invasive technique that is conducted cost-effective and available at many health care services for nutritional assessment and anthropometric analysis including percentages of fat, protein, body fluid, and minerals in human bodies. Previous studies already showed the relationships between body compositions including sarcopenia using skeletal muscle index, visceral fat and phase angle and clinical and oncologic outcomes of CRC (17-20). However, there were no studies to find the effects of visceral fat on clinical, pathologic and oncologic outcomes about CRC using BIA, so far. Therefore, our study aimed to compare the impacts of visceral fat measuring by bioelectrical impedance analysis on clinical, pathologic and oncologic outcomes to patients who was underwent surgical treatment for CRC.

2. Materials and methods

2.1. Patients and data collection

This study was approved by the Institutional Review Board of the Dongsan Medical Center (Daegu, Republic of Korea, IRB No. 2022-07-015). The need for informed conset was waived in this retrospective study. The study group included 204 patients who underwent laparoscopic surgery for colorectal cancer between January 2016 and June 2020. The exclusion criteria included synchronous or previous malignancies, malignancies other than adenocarcinoma, and familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer and presented in Figure 1.

2.2. Data collection and definitions

A prospectively maintained database and electronic medical record were searched to collect data. Data on patient demographics, including age, sex, American Society of Anesthesiology (ASA) score,

preoperative carcinoembryonic antigen (CEA), body mass index (BMI), and location of the tumor, biomarker of immune and inflammation including platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), platelet-neutrophil index (PNI) and pan-immune inflammation value (PIV) were collected retrospectively using electric medical record. 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, tumor size, lymphovascular invasion, perineural invasion from medical records. Body compositions were also included phase angle, appendicular skeletal muscle mass (ASM), skeletal muscle index (SMI), body fluid, intracellular fluid, extracellular fluid, and body fat mass measure by BIA. The 8^{th} edition of the American Joint Committee on Cancer classification system was used to determine the pathological tumor depth, the number of metastasized lymph nodes, and cancer stage. A postoperative clinical examination, measurement of serum CEA levels, chest radiography every 3 months, and chest/abdominal CT every 6 months were performed during each follow-up examination over a period of 3 years. After 3 years, the follow-up interval was changed to 6 months. Recurrence was defined as the presence of radiologically

confirmed or histologically proven tumor. Location of recurrence was defined as the first site of recurrence after complete resection. Local recurrence was defined as any tumor recurrence in the surgical field; local recurrence with synchronous systemic recurrence included systemic recurrence. Overall survival (OS) was defined as the time from the date of surgery to the date of the latest follow-up visit or the date of death due to any cause, and disease-free survival (DFS) was defined as the time from surgery to any type of recurrence.

2.3. Preoperative evaluation and surgical treatment

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

2.4. Bioelectrical Impedance analysis (BIA)

BIA was performed using Inbody 770 (Biospace, Republic of Korea) to estimate patients' 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. Skeletal muscle index (SMI) was calculated using Baumgartner's definition (appendicular/height^2).

2.5. Assessment of hematologic parameters and inflammation-based prognostic scores

During preoperative work-up, patients' blood samples were collected just before their surgery to investigate the hematologic parameters, including hemoglobin, white blood cell (WBC), hemoglobin, platelet, and albumin. A complete blood cell count was performed on these blood samples to calculate the PLR, NLR, PNI, and PIV. The PLR was calculated as the absolute count of platelets divided by the absolute count of

lymphocytes. Patients were divided into the low and high PLR groups using a cutoff value of 150 (9). In addition, other inflammation-based prognostic scores were calculated (PNI: 10× serum albumin concentration (g/dL) + 0.005 × absolute lymphocyte count; NLR: absolute neutrophil count/absolute lymphocyte count). The PIV was developed as a novel biomarker that incorporates all inflammatory cellular components, including neutrophils, lymphocytes, platelets and monocytes (18). Preoperative PIV was calculated using the following formula (absolute neutrophil count × platelet count × absolute monocyte count / absolute lymphocyte count).

2.6. Statistical analysis

The results are presented as average with ranges for standard deviations 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 using independent t-test and Mann-Whitney U test. A p-value < 0.05 was considered to indicate statistical significance. Owing to the asymptotic distribution of our data, optimal cut-off value of visceral fat area in our study was estimated using *Contal and O'Quigley method*

(19). The *Contal and O'Quigley method* is used to identify cut points in continuous variables in survival analysis. The method involves calculating all log-rank statistics, and selecting the optimal cut-off point based on maximizing the log-rank statistics. This method was used for every possible cut-off, and the one with the largest Q statistic was selected for further analysis. Events of the *Contal and O' Quigley equations* were included in mortality and recurrence.

The overall survival curves and disease-free survival curves were evaluated using Kaplan-Meier method using the log-rank test for univariate analysis. Cox proportional hazards models were used to test whether adiposity influences DFS. The effects of individual variables on patient survival were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical analyses were performed with IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline characteristics of patients

We defined the cut-off values of visceral fat area based on disease-free survival using using *Contal and O'Quigley method.* VFA ≥ 67.7cm^2 was defined as high visceral fat area. Based on these cut-off values, 85 (41.7%) patients had low VFA and 119 (58.3%) patients had high VFA. Patient and tumor characteristics according to low and high adiposity are shown in Table 1. Percentages of male were higher in low VFA patients than high VFA patients (77.6% vs. 62.2%; $p < 0.05$). Patients with high VFA showed higher preoperative C-reactive protein and BMI than patients with low VFA (0.8 ± 1.7 vs. 0.4 ± 0.7, $p < 0.05$ and 25.0 ± 2.6 vs. 21.3 ± 1.8; $p < .001$, respectively). There was no significant difference in age, preoperative CEA, ASA groups, and location of tumor between two groups. Immune-inflammatory prognostic markers including PLR, NLR, PNI, and PIV showed no significant differences between two groups.

3.2. Perioperative clinical outcomes

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

3.3. Postoperative pathologic outcomes

Table 3 shows postoperative pathologic outcomes. There were no significant differences in tumor and nodal stage, number of retrieved lymph nodes, proportion of lymph nodes acquired more than 12, number of positive lymph nodes, tumor size, lymphovascular invasion, and perineural invasion between low and high VFA groups. Patients with high VFA showed more moderately differentiation and poorly differentiation than patients with low VFA (90.6% vs. 83.3% and 6.8% vs. 4.8%; $p < 0.05$).

3.4. Inbody 770 body composition analysis of patients

Table 4 showed the body composition analysis of patients between low VFA and high VFA patients using Inbody 770. Patients with high VFA had higher weight compared to patients with low VFA (66.2 ± 11.2 vs. 56.4 ± 7.8; $p < 0.001$). Other body compositions including phase angle, appendicular skeletal muscle mass and skeletal muscle index 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 (20.3 ± 4.8 vs. 11.6 ± 2.6; $p < 0.001$).

3.5. Oncologic outcomes

Median follow up period were 35.6 months in low VFA groups and 40.0 months in high VFA groups without significant differences. High VFA groups showed poor prognosis about 5 year overall survival and disease free survival, but there were no statistical differences (88.3% vs.

90.3%; p=0.909 and 79.8% vs. 89.3%; p > 0.05). There were three cases of recurrence in low VFA and fourteen cases of recurrence in high VFA groups. All of recurrence were included in systemic recurrence in low VFA groups, but nine cases of systemic recurrence and five cases of local recurrence were developed in high VFA groups. In low VFA groups, two patients had liver recurrence and one patient showed peritoneal seeding. Three patients showed liver recurrence, three patients showed lung recurrence, one patient showed bone metastasis and two patients showed peritoneal seeding. Figure 2 and 3 shows the relationship between VFA and long-term survival using the Kaplan-Meier curve. Overall survival and disease-free survival was better in patients with low VFA without statistical differences (OS 90.3% vs. 88.3%; p > 0.05, DFS 89.3% vs. 79.8%; p > 0.05) and shown in Figure 2 and 3.

3.6. Univariate and multivariate survival analyses of prognostic factors

In univariate analyses revealed that preoperative CRP, lymph nodal status, perineural invasion, and PIV were identified as a significant prognostic factors for OS. Sex, tumor and nodal status, perineural

invasion were identified as a significant prognostic factors for DFS. To examine the independent role of VFA in postoperative prognosis, we conducted a multivariate survival analysis using Cox proportional hazard analysis including indexes which were shown statistical differences in univariate analysis. In the multivariate analysis, after adjusting for Sex, sarcopenia, preoperative CEA, preoperative CRP, PIV, T stage, N stage, lymphovascular invasion, and perineural invasion, patients with high VFA showed a significant relationship with poorer DFS (HR 4.26; 95% CI 1.28-14.20; $p < 0.05$) compared with the low VFA group as reference. Patients with higher preoperative CRP showed a significant relationship with poor OS (HR 3.88; 95% CI 1.00-15.05; $p < 0.05$) and N stage showed greater risk factor of mortality to those with low VFA (HR 8.00; 95% CI 1.41-45.21; $p < 0.05$). Female Sex showed preventive index in disease free survival (HR 0.11; 95% CI 0.01-0.91; $p < 0.05$), but patients with lymphovascular invasion showed poor prognosis (HR 3.56; 95% CI 1.10-11.54; $p < 0.05$).

4. Discussions

This study demonstrated that high visceral fat adiposity preoperatively measured by BIA was associated with higher preoperative CRP and poorer histologic differentiation in patients with CRC who underwent curative resection. In the multivariate analysis for oncologic outcomes, visceral fat was independent prognostic factor for DFS. In contrast, VFA was not significantly linked with short-term clinical and pathologic outcomes, immune-inflammatory prognostic indicators, or other body compositions including skeletal muscle index, body fluid, and phase angle.

Several studies have shown that operation time was longer and postoperative complications occur frequently after surgery in high VFA patients (13, 14). A recent meta-analysis that aimed to determine the impact of VFA on laparoscopic CRC surgery showed that visceral obesity was associated with increased surgical difficulty and post-operative morbidity (23). However, other recent study concluded that there were no significant relationship between visceral fat and intraoperative difficulties and postoperative complications (24). In this study, there

were no significant difference in perioperative short-term outcomes including total operation time, recovery-related outcomes, and postoperative complications between low and high VFA patients. We think that factors other than visceral obesity have a greater impact on perioperative outcomes in our study. Future research will require further studies, such as multivariate analysis on perioperative outcomes.

In cancer-free individuals, elevated levels of CRP are associated with an increased risk of all types of cancer, lung cancer, and possibly colorectal cancer (25). Elevated CRP was well-known risk factor of several cancers and poor prognostic value in colorectal cancers (26,27). In our study, preoperative elevated CRP was associated with high VFA and investigated as an independent poor prognostic factor for OS in line with previous studies. Previous studies showed the significant correlation between CRP and visceral adiposity (28,29). Based on previous research and our own findings, it can be suggested that visceral adipose is associated with chronic cancer inflammation.

Regarding the clinical significance of visceral fat in relation to oncologic outcome, several studies have produced contradictory findings. Park et al. reported that high VFA patients showed lesser lymph node metastasis or lower metastatic lymph node ratio (MLR), however there was no association between VFA and overall survival of

CRC patients (16). In contrast, other studies have found a significant association between high VFA and poor oncologic outcomes (30,31). In the current study, univariate analysis revealed no statistically significant differences between the high and low VFA groups in terms of oncologic outcomes, however it was investigated as an independent prognostic factor for DFS in the multivariate analysis. In general, female is well-known good prognostic factor for colorectal cancer (32,33). Our study showed that females were analyzed as independent prognostic factors for DFS with an HR of 0.11 compared to males. In univariate analysis, the prognostic impact of VFA on DFS was offset by the good prognostic factor of female. However, in multivariate analysis, the prognostic impact of VFA was analyzed as an independent poor prognostic factor.

Several studies have provided the evidence of significant contribution of visceral obesity to cancer development and showed the role of omental fat in intraperitoneal tumorigenesis which was associated systemic recurrence of CRC (34,35) Park et al. showed the association with higher visceral adipocyte and higher risk of peritoneal seeding in recurred colorectal cancer (36). Regarding mechanisms of colorectal cancer development, previous research demonstrated that visceral adipocytes contained elevated levels of inflammatory lipid metabolism markers, some of which were associated

with CRC tumor stage, and that obesity-induced chronic low-grade inflammation induces oxidative stress factors (14,37). The major product of lipid peroxidation is 4-hydroxynonenal (HNE) and it is responsible of de-regulation of multiple pathways involved in cell proliferation and differentiation, cell survival, apoptosis and necrosis. The molecular pathways mainly altered by 4-HNE includes mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3KCA) / protein kinase B (AKT) signaling pathway and nuclear factor kappa B (NF-κB). Moreover, accumulation of DNA mutations, as in APC, KRAS, NRAS, BRAF, or PIK3CA sets obesity as a multifactor phenomenon involved in CRC initiation and progression (14).

There have been numerous studies on the effect of visceral fat composition on the clinical and oncological outcomes of colorectal cancer using dual energy X-ray absorptiometry or CT (13,14,23,38-41). However, measuring the area of visceral fat using CT or DEXA scan is a time-consuming task and requires a specific program (39,40). On the other hand, BIA is a noninvasive, cost-effective, and widely accessible method for nutritional evaluation and anthropometric measurement that is performed by clinicians and health provider. Recently, Several research have established validity for evaluating body fat composition using BIA against CT scan, and these studies have demonstrated good concordance between BIA and CT scan (42-44). A prospective cohort study

a high body fat percentage measured by BIA was found to be associated with increased risk of advanced CRC tumor, particularly in men (45). We expect that research on body fat components and colorectal cancer utilizing BIA will continue vigorously.

Nevertheless, out study has some limitations. This study includes its retrospective design, which bears the issue of incomplete data and potential selection bias in single center study. Although our cut-off values might be suitable for Asian ethnic groups, there may be some difficulties in adopting our results in different ethnic groups. Additionally, the median follow-up period of patients participating in this study had a relatively short follow-up period of 35 months at low VFA and 40 months at high VFA, so there was a limit to analyzing long-term oncological outcome.

5. Summary

We investigated the correlation with VFA and clinical, pathologic, and oncologic outcomes of CRC. In multivariate analysis using Cox proportional hazard model, VFA was associated with higher risk of DFS and high VFA patients showed high preoperative CRP and poorer histologic differentiation. But, there were no significant effects on other clinical and nutritional outcomes. Our study suggests using BIA to quantify visceral fat can be used to identify the prognosis of colorectal cancer patients.

References

1. Islami F, Ward EM, Sung H, Cronin KA, Tangka FKL, Sherman RL, et al: Annual Report to the Nation on the Status of Cancer, Part 1. National Cancer Statistics. J Natl Cancer Inst 2021.

2. Bluher M: Obesity: lobal epidemiology and pathogenesis. Nat Rev Endocrinol 2019;15:288-98.

3. Bardou M, Barkun AN, Martel M: Obesity and colorectal cancer. Gut 2013;62:933-47.

4. Jochem C, Leitzmann M: Obesity and Colorectal Cancer. Recent Results Cancer Res 2016;208:17-41.

5. Perez-Hernandez AI, Catalan V, Gomez-Ambrosi J, Rodriguez A, Fruhbeck G: Mechanisms linking excess adiposity and carcinogenesis promotion. Front Endocrinol (Lausanne) 2014;5:65.

6. Murphy TK, Calle EE, Rodriguez C, Kahn HS, Thun MJ: Body mass index

and colon cancer mortality in a large prospective study. Am J Epidemiol 2000;152:847-54.

7. Calle EE, Kaaks R. Overweight: obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579-91.

8. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M: Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371:569-78.

9. Examination Committee of Criteria for 'Obesity Disease' in J, Japan Society for the Study of O: New criteria for 'obesity disease' in Japan. Circ J 2002;66:987-92.

10. Consultation WHOE: Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63.

11. Goulart A, Malheiro N, Rios H, Sousa N, Leao P: Influence of Visceral Fat in the Outcomes of Colorectal Cancer. Dig Surg 2019;36:33-40.

12. Martinez-Useros J, Garcia-Foncillas J: Obesity and colorectal cancer: molecular features of adipose tissue. J Transl Med 2016;14:21.

13. Ballian N, Lubner MG, Munoz A, Harms BA, Heise CP, Foley EF, et al: Visceral obesity is associated with outcomes of total mesorectal excision for rectal adenocarcinoma. J Surg Oncol 2012;105:365-70.

14. Park SW, Lee HL, Doo EY, Lee KN, Jun DW, Lee OY, et al: Visceral Obesity Predicts Fewer Lymph Node Metastases and Better Overall Survival in Colon Cancer. J Gastrointest Surg 2015;19:1513-21.

15. Vergara-Fernandez O, Trejo-Avila M, Salgado-Nesme N: Sarcopenia in patients with colorectal cancer: A compr.hensive review. World J Clin Cases 2020;8:1188-202.

16. Charette N, Vandeputte C, Ameye L, Bogaert CV, Krygier J, Guiot T, et al: Prognostic value of adipose tissue and muscle mass in advanced colorectal cancer: a post hoc analysis of two non-randomized phase II trials. BMC Cancer 2019;19:134.

17. Gupta D, Lammersfeld CA, Burrows JL, Dahlk SL, Vashi PG, Grutsch JF, et al: Bioelectrical impedance phase angle in clinical practice:

implications for prognosis in advanced colorectal cancer. Am J Clin Nutr 2004;80:1634-8.

18. Fuca G, Guarini V, Antoniotti C, Morano F, Moretto R, Corallo S, et al: The Pan-Immune-Inflammation Value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled-analysis of the Valentino and TRIBE first-line trials. Br J Cancer 2020;123:403-9.

19. Geiger JT, Aquina CT, Esce A, Zhao P, Glocker R, Fleming F, et al: One-year patient survival correlates with surgeon volume after elective open abdominal aortic surgery. J Vasc Surg 2021;73:108-16 e1.

20. Yang T, Wei M, He Y, Deng X, Wang Z: Impact of visceral obesity on outcomes of laparoscopic colorectal surgery: a meta-analysis. ANZ J Surg 2015;85:507-13.

21. Yu H, Joh YG, Son GM, Kim HS, Jo HJ, Kim HY: Distribution and Impact of the Visceral Fat Area in Patients With Colorectal Cancer. Ann Coloproctol 2016;32:20-6.

22. Tsilidis KK, Branchini C, Guallar E, Helzlsouer KJ, Erlinger TP, Platz EA: C-reactive protein and colorectal cancer risk: a systematic

review of prospective studies. Int J Cancer 2008;123:1133-40.

23. Zhou B, Shu B, Yang J, Liu J, Xi T, Xing Y: C-reactive protein, interleukin-6 and the risk of colorectal cancer: a meta-analysis. Cancer Causes Control 2014;25:1397-405.

24. Liao CK, Yu YL, Lin YC, Hsu YJ, Chern YJ, Chiang JM, et al: Prognostic value of the C-reactive protein to albumin ratio in colorectal cancer: an updated systematic review and meta-analysis. World J Surg Oncol 2021;19:139.

25. Allin KH, Bojesen SE, Nordestgaard BG: Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. J Clin Oncol 2009;27:2217-24.

26. Saijo Y, Kiyota N, Kawasaki Y, Miyazaki Y, Kashimura J, Fukuda M, et al: Relationship between C-reactive protein and visceral adipose tissue in healthy Japanese subjects. Diabetes Obes Metab 2004;6:249-58.

27. Tsuriya D, Morita H, Morioka T, Takahashi N, Ito T, Oki Y, et al: Significant correlation between visceral adiposity and high-sensitivity

C-reactive protein (hs-CRP) in Japanese subjects. Intern Med 2011;50:2767-73.

28. Guiu B, Petit JM, Bonnetain F, Ladoire S, Guiu S, Cercueil JP, et al: Visceral fat area is an independent predictive biomarker of outcome after first-line bevacizumab-based treatment in metastatic colorectal cancer. Gut 2010;59:341-7.

29. Basile D, Bartoletti M, Polano M, Bortot L, Gerratana L, Di Nardo P, et al: Prognostic role of visceral fat for overall survival in metastatic colorectal cancer: A pilot study. Clin Nutr 2021;40:286-94.

30. Cheung WY, Shi Q, O'Connell M, Cassidy J, Blanke CD, Kerr DJ, et al: The predictive and prognostic value of sex in early-stage colon cancer: a pooled analysis of 33,345 patients from the ACCENT database. Clin Colorectal Cancer 2013;12:179-87.

31. Yang Y, Wang G, He J, Ren S, Wu F, Zhang J, et al: Sex differences in colorectal cancer survival: A meta-analysis. Int J Cancer 2017;141:1942-9.

32. Xiang F, Wu K, Liu Y, Shi L, Wang D, Li G, et al: Omental adipocytes enhance the invasiveness of gastric cancer cells by oleic acid-induced activation of the PI3K-Akt signaling pathway. Int J Biochem Cell Biol 2017;84:14-21.

33. Nieman KM, Kenny HA, Penicka CV, Ladanyi A, Buell-Gutbrod R, Zillhardt MR, et al: Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Nat Med 2011;17:1498-503.

34. Park JW, Chang SY, Lim JS, Park SJ, Park JJ, Cheon JH, et al: Impact of Visceral Fat on Survival and Metastasis of Stage III Colorectal Cancer. Gut Liver 2022;16:53-61.

35. Liesenfeld DB, Grapov D, Fahrmann JF, Salou M, Scherer D, Toth R, et al: Metabolomics and transcriptomics identify pathway differences between visceral and subcutaneous adipose tissue in colorectal cancer patients: the ColoCare study. Am J Clin Nutr 2015;102:433-43.

36. Furstenberg A, Davenport A: Assessment of body composition in peritoneal dialysis patients using bioelectrical impedance and dual-energy x-ray absorptiometry. Am J Nephrol 2011;33:150-6.

37. Kim M, Shinkai S, Murayama H, Mori S: Comparison of segmental multifrequency bioelectrical impedance analysis with dual-energy X-ray absorptiometry for the assessment of body composition in a community-dwelling older population. Geriatr Gerontol Int 2015;15:1013-22.

38. Lee DH, Park KS, Ahn S, Ku EJ, Jung KY, Kim YJ, et al: Comparison of Abdominal Visceral Adipose Tissue Area Measured by Computed Tomography with That Estimated by Bioelectrical Impedance Analysis Method in Korean Subjects. Nutrients 2015;7:10513-24.

39. Kim SS, Kim JH, Jeong WK, Lee J, Kim YK, Choi D, et al: Semiautomatic software for measurement of abdominal muscle and adipose areas using computed tomography: A STROBE-compliant article. Medicine (Baltimore) 2019;98:e15867.

40. Silva A, Faria G, Araujo A, Monteiro MP: Impact of adiposity on staging and prognosis of colorectal cancer. Crit Rev Oncol Hematol 2020;145:102857.

41. Brandstedt J, Wangefjord S, Nodin B, Gaber A, Manjer J, Jirstrom K. Sex: anthropometric factors and risk of colorectal cancer with particular reference to tumour location and TNM stage: a cohort study.

Biol Sex Differ 2012;3:23.

Impact of Visceral Fat Area Measured by Bioelectrical Impedance Analysis (BIA) on Clinicopathologic and Cncologic Outcomes of Coloretcal Surgery

Kim, Kyeong Eui

Department of Medicine

Graduate School Keimyung University

Supervised by Professor Sung Uk Bae

(Abstract)

Although visceral fat adiposity has known to be associated with clinical, pathologic, and oncologic outcomes in patients with colorectal cancer (CRC), the clinical significance was inconsistent. We investigated clinical and pathologic outcomes and prognostic impact of visceral fat adiposity in patients with CRC after surgical resection using BIA. This retrospective single center study included 204 patients who underwent surgery for CRC between January 2016 and June 2020. Visceral fat area (VFA) was measured by BIA using Inbody 770 (Biospace, Republic of Korea). Optimal cut-off value for VFA was defined using *Contal and O'Quigley method.* The Cox proportional hazards model was used to determine the correlation VFA and disease-free survival (DFS). Female patients were more frequently in high VFA patients. Preoperative C-reactive protein (CRP) was higher in high VFA patients. Also, high

VFA showed poorer histologic differentiation. In univariate analysis, high VFA was tended to poorer prognostic value in DFS. However, multivariate analysis revealed that high VFA independently predicted poorer DFS. High VFA was correlated with poorer DFS in CRC. Elevated preoperative CRP and poor histologic differentiation was related to high VFA. However, there were no significant differences on other clinical and pathologic outcomes in CRC.

생체 전기 임피던스 분석으로 측정한 내장 지방 단면적이 대장 수술의 임상병리학적, 종양학적 결과에 미치는 영향

김 경 의

계명대학교 대학원

의학과

(지도교수 배 성 욱)

(초록)

내장 지방 단면적은 대장암 환자에서 임상적, 병리학적 그리고 종양학적 예후와 연관성이 있다고 알려져 있습니다. 하지만, 그 결과가 일치하지는 않았습니다. 본 연구는 대장암 수술을 받은 환자들에게 내장 지방 단면적이 임상병리학적, 종양학적으로 미치는 영향을 확인하고자 진행되었습니다. 본 연구는 후향적 연구로 진행되었으며 본 의료원에서 2016년 1월부터 2020년 6월까지 대장암으로 수술적 치료를 받은 204 명을 포함하였습니다. 내장 지방 단면적은 Inbody 770 (Biospace, 대한민국)을 이용한 생체 전기 임피던스 분석으로 측정되었습니다. 본 연구에 사용된 내장 지방 단면적의 기준점은 *Contal and O'Quigley* 방법을 이용하여 정의되었습니다. 콕스 비례위험모형을 이용하여 내장 지방 단면적과 무병생존율과의 연관성을 확인하였습니다. 본 연구에서 여성 환자들이 더 높

은 내장 지방 단면적을 가지고 있었습니다. 수술 전 C-반응 단백질은 높은 내장 지방 단면적을 가진 환자들에게 더 높았습니다. 또한, 높은 내장 지방 단면적은 저분화 선암종의 발생 빈도와 연관성이 있었습니다. 단변량 분석에서는 높은 내장 지방 단면적을 가지는 것이 무병 생존율에 대한 좋지 못한 예측 인자의 경향을 보였으나 다변량 분석에서는 높은 내장 지방 단면적이 좋지 못한 무병 생존율을 예측하는 독립적인 지표임을 알 수 있었습니다. 대장암으로 수술을 받은 환자들에게 높은 내장 지방 단면적은 좋지 못한 무병 생존율을 예측하는 인자임을 알 수 있었습니다. 또한 높은 내장 지방 단면적은 수술 전 상승된 C 반응단백질과 저분화 선암종의 발생빈도와 연관성이 있었습니다. 하지만 그 이외의 임상병리학적 결과에서는 내장 지방 단면적이 미치는 별다른 영향을 확인하지 못하였습니다.

Table 1. Patient and Tumor Characteristics

	Low VFA (n=85)	High VFA (n=119)	p value
Age (year)	65.9±9.7	66.0±10.2	0.929
Sex			0.019
Male	66 (77.6)	74 (62.2)	
Female	19 (22.4)	45 (37.8)	
Preoperative CEA (ng/mL)	7.0±20.7	5.4±16.0	0.552
Preoperative CRP	0.4±0.7	0.8±1.7	0.047
ASA groups			0.827
I	26 (30.6)	33 (27.7)	
II	49 (57.6)	69 (58.0)	
III	26 (30.6)	33 (27.7)	
BMI (kg/m^2)	21.3±1.8	25.0±2.6	<0.001
Location of tumor			0.599
Right	22 (25.9)	27 (22.7)	
Left	63 (74.1)	92 (77.3)	
Hemoglobin (g/dl)	12.6±2.0	12.4±1.7	0.609
Platelet ($x10^3$)	246.2±71.8	241.4±72.3	0.636
WBC ($x10^3$)	6.4±2.1	6.0±1.9	0.105
PLR	181.7±114.6	188.2±102.2	0.677
NLR	3.3±3.8	3.1±2.5	0.636

PNI	66.9±27.7	71.2±30.8	0.305
PIV	383.1±710.2	276.9±294.7	0.196
Albumin (g/dl)	4.2±0.5	4.2±0.4	0.603

Values are presented as mean ± standard deviation or number (%). ASA: American society of anesthesiologists; BMI: Body mass index; CEA: Carcinoembryonic antigen; CRP: C-reactive protein; NLR: Neutrophil lymphocyte ratio; PIV: Pan-immune inflammation value; PLR: Platelet-lymphocyte ratio; PNI: Prognostic nutritional index; VFA: Visceral fat area; WBC: White blood cell

Table 2. Perioperative Clinical Outcomes

	Low VFA (n=85)	High VFA (n=119)	p value
Operation time (min)	209.3±112.1	204.0±86.2	0.711
Time to gas out (d)	3.2±2.2	4.0±4.8	0.319
Time to sips of water (d)	4.0±3.1	4.0±4.8	0.983
Time to soft diet (d)	6.3±3.2	6.6±5.1	0.603
Time to hospital stay (d)	10.4±6.4	10.2±6.2	0.773
Morbidity within 30 days after surgery	28 (32.9)	40 (33.6)	0.920
Clavien-dindo classifications > 3a	17 (20.0)	25 (21.0)	0.861

Values are presented as mean±standard deviation or number (%). d: day; min: minute; VFA: visceral fat area

Table 3. Postoperative Pathologic Outcomes

	Low VFA (n=85)	High VFA (n=119)	p value
Tumor stage			0.114
T1	16 (18.8)	33 (24.0)	
T2	16 (18.8)	42 (20.6)	
T3	43 (50.6)	99 (48.5)	
T4	10 (11.8)	14 (6.9)	
Nodal stage			0.945
N0	55 (64.7)	79 (66.4)	
N1	21 (24.7)	27 (22.7)	
N2	9 (10.6)	13 (10.9)	
Histology			0.027
Well differentiated	10 (11.9)	3 (2.6)	
Moderately differentiated	70 (83.3)	106 (90.6)	
Poorly differentiated	4 (4.8)	8 (6.8)	
Retrieved LNs	19.5±9.4	18.1±9.2	0.310
LN > 12	77 (90.6)	99 (83.2)	0.130
Positive LNs	1.0±2.0	0.9±2.1	0.807
Tumor size (cm)	3.9±2.1	3.5±2.1	0.211
Lymphovascular invasion	27 (31.8)	27 (23.5)	0.192

Perineural invasion	16 (19.3)	25 (22.5)	0.584

Values are presented as mean ± standard deviation or number (%). LN: Lymph node; VFA: Visceral fat area

Table 4. Inbody 770 Body Composition Analysis of Patients

	Low VFA (n=85)	High VFA (n=119)	p value
Height (cm)	162.3±8.6	162.4±9.5	0.980
Weight (kg)	56.4±7.8	66.2±11.2	<0.001
Phase angle (‘)	5.1±0.6	5.0±0.7	0.629
ASM (kg)	7.0±1.1	7.1±1.1	0.650
SMI (kg/m^2)	2.7±0.5	2.7±0.4	0.749
Body fluid	33.1±5.3	33.9±6.7	0.347
ICF (%)	20.3±3.4	20.8±4.2	0.362
ECF (%)	12.8±2.0	13.1±2.6	0.328
BFM (kg)	11.6±2.6	20.3±4.8	<0.001

Values are presented as mean±standard deviation or number(%). ASM: Appendicular skeletal muscle mass; BFM = Body fat mass; ECF: Extracellular fluid; ICF: Intracellular fluid; SMI: Skeletal muscle index; VFA: Visceral fat area

Table 5. Oncologic Outcomes

	Low VFA (n=85)	High VFA (n=119)	p value
Median follow-up (months)	35.6±16.2	40.0±18.0	0.073
5-yr OS (%)	90.3	88.3	0.909
5-yr DFS (%)	89.3	79.8	0.105
Recurrence	3	14	
Recurrence pattern			0.070
Systemic recurrence	3	9	
Local recurrence	0	5	

Values are presented as mean±standard deviation or number(%); DFS: disease free survival; OS: Overall survival; VFA: Visceral fat area

Table 6. Prognostic Factors of 5-year Survival by Univariate Analysis

Prognostic factor	N	OS (5 years, %)	Log Rank p-value	DFS (5 years, %)	Log Rank p-value
Visceral fat area			0.909		0.105
Low	85	90.3		89.3	
High	119	88.3		79.8	
Age			0.689		0.917
≤ 65	89	90.2		84.7	
> 65	115	87.8		82.1	
Sex			0.060		0.016
Male	140	85.5		79.5	
Female	64	96.9		92.0	
BMI			0.332		0.327
High (>25)	52	92.8		90.2	
Low (<25)	152	87.5		80.8	
ASA score			0.253		0.571
1	59	94.9		81.9	
2 & 3	145	86.6		84.0	
Sideness			0.431		0.687
Right sided	49	84.2		79.4	
Left sided	155	90.6		84.7	
Pre-op CEA (ng/ml)			0.164		0.072

< 5	162	90.6		85.0	
≥5	42	82.2		76.7	
Pre-op CRP (mg/l)			0.043		0.623
< 0.3	99	90.0		86.6	
≥0.3	55	80.3		83.7	
Tumor stage			0.119		0.037
T1 & T2	91	92.8		92.0	
T3 & T4	113	85.6		76.0	
Nodal stage			<0.001		0.001
Nodal negative	133	94.5		90.4	
Nodal positive	71	79.0		69.5	
Differentiation			0.822		0.488
Well	15	92.9		92.9	
Moderate & poor	188	89.1		83.0	
Lymphovascular invasion			0.085		0.089
No	146	90.8		84.8	
Yes	54	83.3		78.3	
Perineural invasion			0.030		0.004
No	153	92.1		85.5	
Yes	41	80.6		72.6	
LN harvest			0.314		0.363
≥12	176	88.3		82.2	
< 12	28	92.3		92.9	

PIV			0.010		0.298
Low	145	94.1		86.1	
High	59	77.3		77.1	
Phase angle			0.215		0.944
Low	117	92.1		85.3	
High	87	84.3		82.4	
Sarcopenia			0.311		0.313
No	143	90.3		85.0	
Yes	61	85.6		79.4	

ASA: American society of anesthesiologists; BMI: Body mass index; CEA: Carcinoembryonic antigen; CRP: C-reactive protein; LN: Lymph node; PIV: Pan-immune inflammation value;

Table 7. Prognostic Factors of Overall Survival and Disease-Free Survival in Multivariate Analysis

Variables	Reference category	Overall Survival		Disease-free survival	
		HR (95% CI)	p-value	HR (95% CI)	p-value
VFA					
High	Low	1.67 (0.50 - 5.56)	0.401	4.26 (1.28 - 14.20)	0.018
Sex					
Female	Male	0.59 (0.12 - 2.87)	0.509	0.11 (0.01 - 0.91)	0.040
Sarcopenia					
Yes	No	1.57 (0.49 - 5.08)	0.451	2.31 (0.79 - 6.77)	0.126
Pre-OP CEA					
≥5	<5	0.96 (0.29 - 3.16)	0.942	0.92 (0.28 - 3.04)	0.890
CRP					
≥0.3	<0.3	3.88 (1.00 - 15.05)	0.050	1.38 (0.44 - 4.35)	0.585
PIV					
High	Low	1.17 (0.316 - 4.356)	0.811	0.62 (0.19 - 2.03)	0.426
Tumor stage					
T3, T4	T1, T2	0.91 (0.14 - 6.08)	0.926	1.11 (0.27 - 4.63)	0.889
Nodal stage					
N1, N2	N0	8.00 (1.41 - 45.21)	0.019	1.28 (0.37 - 4.45)	0.702
Lymphovascular invasion					
Yes	No	3.06 (0.88 - 10.63)	0.078	3.56 (1.10 - 11.54)	0.034

Perineural invasion					
Yes	No	1.10 (0.31 - 3.95)	0.880	2.46 (0.73 - 8.25)	0.144

CEA: Carcinoembryonic antigen; CRP: C-reactive protein; PIV: Pan-immune inflammation value; VFA: Visceral fat area

Figure 1. Flow Chart of the Study

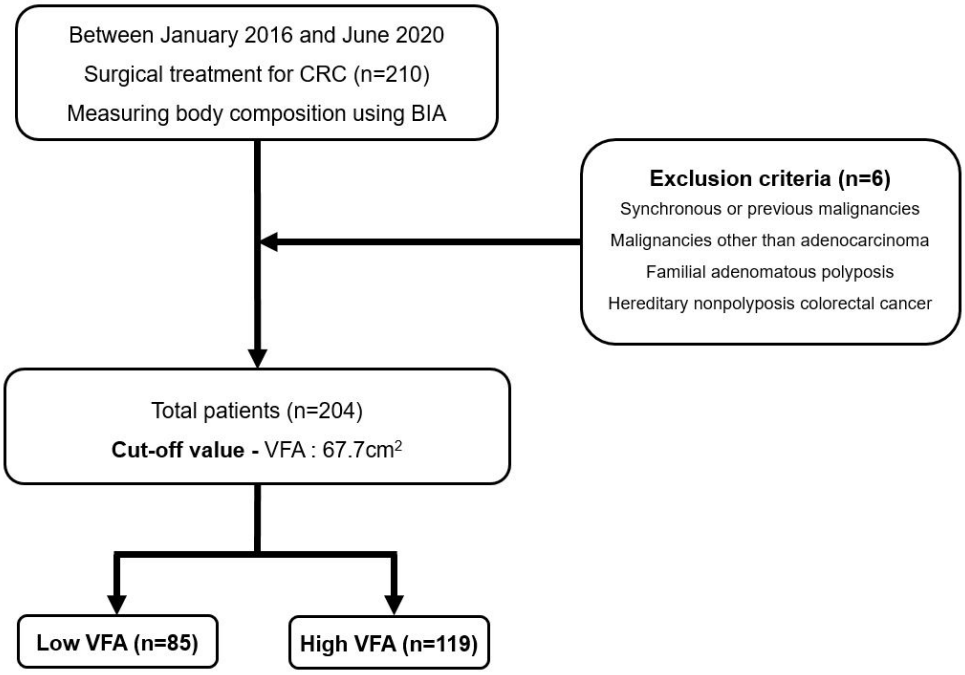

Figure 2. Kaplan-Meier Survival Curve for the Cumulative Risk of Overall survival

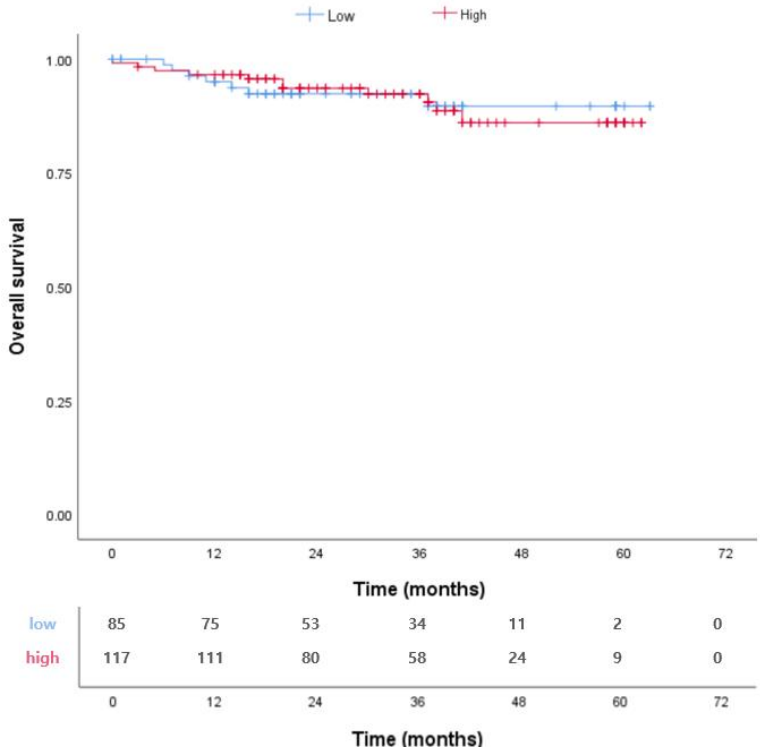

Figure 3. Kaplan-Meier Survival Curve for the Cumulative Risk of Disease-Free Survival