Prognostic Impact of Changes in Adipose Tissue Areas after Colectomy in Colorectal Cancer Patients

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ORIGINAL ARTICLE

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There have been few studies assessing the changes in the body components of patients after colectomy in colorectal cancer (CRC). The purpose of this study was to verify the trends in the adipose tissue areas of CRC patients before and after surgery and to determine their clinical relevance. Computed tomography (CT)-assessed subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) areas were recorded before and after curative resection in stage I to III CRC patients. Changes in the adipose tissue were assessed by calculating the difference in the adipose tissue area between preoperative CT and the most recent postoperative CT, which is disease-free state. Regarding obesity before surgery, there were no prognostic effect of body mass index (BMI), VAT and SAT, and 47.3% of patients had increases in VAT after colectomy. By multivariate analysis, adjusting sex, age, stage, differentiation, VAT change was the only obesity related factor to predict the prognosis, that patients who had increase in VAT after colectomy had better overall survival (HR, 0.557; 95% CI, 0.317-0.880) and disease-free survival (HR, 0.602; 95% CI, 0.391-0.927). BMI and SAT change had no significant association. In subgroup analysis of stage III CRC patients, VAT change had significance for prognosis only in patients who had adjuvant chemotherapy but not in those who did not receive postoperative chemotherapy. Increase in visceral adipose tissue after surgery is a favorable predictor of prognosis for CRC patients.

Keywords: Colorectal Neoplasms; Obesity; Adipose Tissue; Prognosis

INTRODUCTION

Approximately, 20%-30% of colorectal cancer (CRC) patients who undergo curative radical colectomies suffer recurrence (1). Currently, there are no recommendations for patients to reduce their risks of recurrence and mortality after treatment, except for complying with active surveillance. Searching for modifiable factors could provide opportunities for these patients to avoid recurrence and to improve overall survival. There have been several recent studies on the association between obesity and CRC prognosis. However, their results have been inconsistent; although some revealed poorer prognoses for obese patients (2-4), others showed no association (5-7). In such studies, the timing (before or after surgery) and the methods used to define the relationship between obesity and the risk of CRC recurrence or mortality have varied. Few reports have studied the influence of weight change on the risk of recurrence (6,8). Further, the impact of changes in the amount of adipose tissue on recurrence and survival has not been addressed by the existing studies.

We investigated, in a retrospective cohort study, the association between the amount of adipose tissue before and after curative treatment, as well as the links between changes during this time period and CRC survival outcomes. We selected a postoperative timing of more than 1 year after CRC surgery during a sustained period of a disease-free state. Using this timing, we were able to characterize the possible influence of changes in the amount of adipose tissue on cancer cells during the disease-free period.

MATERIALS AND METHODS

Study population

We conducted a retrospective cohort study of CRC patients who underwent curative colectomy performed by the same surgeon at Seoul National University Hospital between October 2004 and December 2008 (n = 701). The cancer stage was determined using the American Joint Committee on Cancer criteria (9). Curative resection included a complete excision of the tumor proximally, distally and circumferentially, as confirmed by a lack of tumor cells at the resection margin, conventional lymph node dissection and no remaining macroscopic evidence of disease. Because all of the operations were performed by the same surgeon, the patients were not affected by inter-surgeon variability. Overall, 630 patients remained after the application of the following exclusion criteria: TNM stage IV tumors; operative meth
ods including total colectomy or transanal excision; extent of colon resection (10) of R1 (all gross disease resected by en bloc resection with margins histologically positive for disease) or R2 (residual gross disease remaining unresected) (11); preoperative neoadjuvant chemoradiation therapy; a history of colon disease, including CRC and inflammatory bowel disease; a family history of CRC; and a cancer treatment history in any organ. For all of the patients eligible for the study, electronic or paper medical records were reviewed. Informations on the patient’s age, year of surgery, pathologic stage, tumor location and postoperative adjuvant treatment were collected.

**Definitions and exposure measurements**

All of the CRC patients underwent preoperative abdominal computed tomography (CT) for staging work-up. Body mass index (BMI) was calculated using recorded body weight (kg) and height (m) before surgery. BMI greater than 25 kg/m² was defined as obese BMI. Postoperative surveillance with abdominal CT, colonoscopy and Carcinoembryonic antigen was started one year after surgery and was repeated annually for 5 years. In this retrospective study, we evaluated the most recently assessed abdominal CT during the recurrence-free follow-up, which was defined as more than 1 year after surgery or more than one year after the completion of adjuvant therapy. Postoperative assessment windows for the CT scan were selected to allow sufficient time after the completion of treatment for the patients to return to their usual bodily states and to avoid any biases caused by wasting cachexic effects or possible adipose tissue area losses immediately before recurrence or death.

The adipose tissue area was measured at the level of the umbilicus, using abdominal CT scanner, as previously described (Fig. 1) (12). We used a commercial software (Rapidia 2.8; FINITT, Seoul, Korea) to measure the pixels density between -250 and -50 Hounsfield units (HU) which defines the fat compartment. We defined visceral adipose tissue (VAT) as an intrabdominal adipose tissue area confined by the parietal peritoneum, excluding the paraspinal muscles and the vertebral column. Subcutaneous adipose tissue (SAT) areas were defined as adipose tissue areas external to the abdomen and back muscles (12). Because there are no standard values for the definition of a normal amount of abdominal adipose tissue, we used the medians of the SAT and VAT areas recorded in this study as references. Obese VAT and obese SAT were defined as values greater than their respective median values (VAT₅₀% and SAT₅₀%).

The changes in the adipose tissue area were calculated by subtracting the adipose tissue area on preoperative abdominal CT from that on postoperative abdominal CT, as described above. Data on the changes in adipose tissue area were available for 548 patients of eligible 630 patients, because some patients underwent surveillance at their local hospitals or experienced recurrence within 1 year after surgery.

**Outcome assessments**

In the analyses of obesity, defined either by BMI or adipose tis-
sue area, and of the changes in adipose tissue area, the primary end-points were disease-free survival (DFS), distant metastasis-free survival (MFS), and overall survival (OS). DFS was defined as the time from the primary operation to cancer recurrence (including local recurrence and distant metastasis) or to the occurrence of a new primary colorectal cancer, and MFS was defined as the time from the primary operation to the detection of distant metastasis. Overall survival (OS) was defined as the time from the primary operation to death from any cause. The data were obtained via linkages with the national death database.

Statistical analyses
Continuous variables are expressed as the means ± standard deviation (SDs). The $\chi^2$ test or Student’s t-test and analysis of variance (ANOVA) for independent samples were used to assess the differences in risk factors between the groups. The effects of the preoperative obesity state, as measured by the SAT and VAT areas, were estimated by calculating hazard ratios (HRs) and 95% confidence intervals (CI), using the Cox proportional hazards model. The effect of adipose tissue area changes, as measured by SAT and VAT area, were also estimated by calculating HRs and 95% CIs. Result were considered statistically significant if $P < 0.05$. All of the statistical analyses were performed using the SPSS software, version 19.0 (SPSS, Chicago, IL, USA).

Ethics statement
The present study protocol was reviewed and approved by the institutional review board of Seoul National University Hospital (IRB number H-1212-099-452). Informed consent was waived by the board.

RESULTS
Baseline characteristics
The eligible group included 405 men (64.2%) and 225 women (35.8%), and the mean age was 62.2 ± 10.5 years old. The median follow-up duration was 67 months (range 13-102 months). Based on BMI, 34.7% were obese. Data on the changes in adipose tissue area were available in 548 patients. The baseline characteristics of the enrolled patients are shown in Table 1 according to the changes in VAT after colectomy. During the postoperative surveillance, 47.3% (259 patients, 176 men and 83 women) of the patients had an increase in VAT amount after colectomy. The VAT-increased group was more likely not to be

| Parameters | VAT decrease (n = 289, 52.7%) | VAT increase (n = 259, 47.3%) | $P$ value |
|------------|-------------------------------|-------------------------------|-----------|
| Sex        | Male:Female 182:107 (63.3:37%) | 176:83 (68.8:32%) | 0.222     |
| Age        | < 65: > 65 yr 153:136 (52.9:47.1) | 150:109 (57.9:42.1) | 0.242     |
| Years (mean ± S.D.*) | 61.61 ± 1.064 | 61.88 ± 0.89 | 0.755      |
| CRC location | Right side:Left side 66:223 (22.8:77.2) | 58:201 (22.4:77.6) | 0.901      |
| Differentiation | W†:M‡:P§:mucinous ll 32:245:7:5 (11.1:84.8:2.4:1.7) | 19:224:15:71 (7.3:86.5:0.4:5.8) | 0.007      |
| T stage    | T1, T2: T3, T4 71:218 (24.6:75.4) | 70:189 (27.7:73) | 0.511     |
| N stage    | N0:N1:N2 163:83:43 (56.4:28.7:14.9) | 163:33:126 (56.4:43.6) | 0.298     |
| Overall stage   | Stage I:II 54:109:126 (18.7:37.7:43.6) | 62:101:96 (23.9:39:37.1) | 0.194     |
| ALI **      | (+):(-):not checked 192:95:2 (66.4:32.9:0.7) | 183:72:4 (70.7:27.8:1.5) | 0.299     |
| VI **       | (+):(-):not checked 259:28:2 (89.6:9.7:0.7) | 235:20:4 (90.7:7.8:1.5) | 0.466     |
| PNI ††       | (+):(-):not checked 238:49:2 (82.3:17:0.7) | 216:39:4 (83.4:15.1:1.5) | 0.541     |
| Current smoker | No:Yes 255:34 (88.2:11.8) | 209:50 (80.7:19.3) | 0.014     |
| Alcohol drinker | No:Yes 188:101 (65.1:34.9) | 177:82 (68.3:31.7) | 0.415     |
| Changes in SAT | Decrease:Increase 155:134 (53.6:46.4) | 49:210 (18.9:81.1) | < 0.001     |
| Adjuvant chemotherapy | Not done:Done 81:208 (28.0:72.0) | 95:164 (36.7:63.3) | 0.030     |

*Standard deviation; †, well differentiated; ‡, moderately differentiated; §, poorly differentiated; ll, mucinous, mucinous cell; ALI, angiolymphatic invasion; VI, venous invasion; PNI, perineural invasion.
poorly differentiated ($P = 0.007$), to smoke ($P = 0.014$) and to have an increase in SAT after the operation ($P < 0.001$). In the analysis of changes in the amount of SAT, 62.8% (344 patients, 223 men and 121 women) of the patients had an increase in SAT amount after colectomy. In the increased SAT group, more advanced pathology (T stage, $P = 0.005$; overall stage, $P = 0.001$) and VAT increases ($P < 0.001$) were observed, compared to the decreased SAT group.

We analyzed the trends in adipose tissue area after colectomy stratified by stages. In stage I, VAT increased in 53.4%, and SAT increased in 50.9%; in stage II, VAT decreased in 51.9%, and SAT increased in 70%. In stage III, VAT decreased in 56.8%, and SAT increased in 63.1%. The total amount of adipose tissue increased in all of the stages.

Impact of adipose tissue amount on cancer recurrence or death

After a mean follow-up of 67 months, of 630 eligible patients, 121 (19.2%) had recurrences (stage I, 15 patients [11.2%]; stage II, 26 [10.9%]; and stage III, 80 [31.1%]), and 101 died (stage I, 8 patients [6%]; stage II, 30 [12.5%]; and stage III, 63 [24.5%]). In univariate analysis, TNM staging, pathological differentiation and VAT changes after colectomy were significantly associated with OS, DFS, and MFS. SAT changes were significant only in DFS. Preoperative obesity status, as defined by VAT, SAT, and BMI, showed no significance in the prediction of OS, DFS or MFS. Kaplan-Meier analysis was performed for stage III patients. The five-year overall survival rate was 72.5% in the VAT-decreased group and 88.0% in the VAT-increased group ($P = 0.001$). The five-year disease-free survival rate was 56.5% in the VAT-decreased group and 74.9% in the VAT-increased group ($P = 0.007$) (Fig. 2).

Since the TNM staging, pathological differentiation and VAT changes were significant in univariate analysis, we performed a multivariate analysis with these factors and other obesity factors under adjustment of sex and age.

The result of the multivariate analysis with TNM stage, differentiation, venous invasion, preoperative VAT, SAT, and BMI obesity status and postoperative changes in VAT and SAT are shown in Tables 2 and 3. For the clinical relevance of the amount of adipose tissue in survival outcomes, VAT change was the only factor that predicted OS, DFS, and MFS. Patients who had an increased VAT after colectomy had better OS (hazard ratio [HR], 0.557; 95% confidence interval [CI], 0.317-0.880), DFS (HR, 0.602; 95% CI, 0.391-0.927), and MFS (HR, 0.652; 95% CI, 0.373-0.906). There were no prognostic effects of preoperative obesity, as defined by VAT, SAT or BMI.

Subgroup analysis of stage III patients

We performed subgroup analysis of stage III patients by perfor-

Table 2. Multivariate Cox proportional hazard model for overall survival

| Category                          | Hazard ratio (95% CI) | P-value |
|-----------------------------------|-----------------------|---------|
| Sex                               |                       |         |
| Female                            | 1                     |         |
| Male                              | 1.050 (0.638-1.729)   | 0.848   |
| Age                               |                       |         |
| < 65 yr                           | 1                     |         |
| > 65 yr                           | 1.232 (0.744-2.041)   | 0.418   |
| Overall stage                     |                       |         |
| Stage I                           | 1                     |         |
| Stage II                          | 1.640 (0.595-4.517)   | 0.002   |
| Stage III                         | 3.887 (1.401-10.781)  |         |
| Differentiation                   |                       |         |
| Well                              | 1                     |         |
| Moderate                          | 1.581 (0.484-5.167)   | 0.012   |
| Poor                              | 9.378 (1.919-45.838)  |         |
| Mucinous                          | 2.021 (0.390-10.469)  |         |
| Venous invasion                   |                       |         |
| Negative                          | 1                     |         |
| Positive                          | 2.922 (1.568-5.445)   | 0.003   |
| By preoperative VAT               |                       |         |
| Not obese                         | 1                     |         |
| Obese                             | 1.132 (0.648-1.977)   | 0.663   |
| By preoperative SAT               |                       |         |
| Not obese                         | 1                     |         |
| Obese                             | 0.800 (0.461-1.389)   | 0.428   |
| VAT change                        |                       |         |
| Decrease                          | 1                     |         |
| Increase                          | 0.557 (0.317-0.880)   | 0.032   |
| SAT change                        |                       |         |
| Decrease                          | 1                     |         |
| Increase                          | 0.765 (0.451-1.296)   | 0.319   |
| By preoperative BMI               |                       |         |
| Not obese                         | 1                     |         |
| Obese                             | 0.802 (0.438-1.468)   | 0.474   |
| Adjuvant chemotherapy             |                       |         |
| Not done                          | 1                     |         |
| Done                              | 0.634 (0.309-1.297)   | 0.212   |

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; BMI, body mass index.
In stage III patients who had postoperative chemotherapy, VAT change was a significant factor that predicted OS (HR, 0.453; 95% CI, 0.213-0.965, \( P = 0.040 \)), DFS (HR, 0.547; 95% CI, 0.310-0.963, \( P = 0.037 \)), and MFS (HR, 0.528; 95% CI, 0.288-0.971, \( P = 0.040 \)) by multivariate analysis. Among stage III patients, 18 patients did not have chemotherapy due to patient’s refusal or old age. On the contrary to chemotherapy-received group, in stage III patients who did not have postoperative chemotherapy, VAT change was not a significant predictor for OS (\( P = 0.979 \)), DFS (\( P = 0.796 \)), and MFS (\( P = 0.796 \)) by multivariate analysis.

**DISCUSSION**

In this retrospective cohort study, an increase in the amount of visceral adipose tissue was associated with better overall survival, disease-survival and distant metastasis-free survival; patients with increased visceral fat after surgery had better surgical outcomes. Compared to the results of several previous studies, the preoperative status of obesity, as defined by VAT and BMI, had no significance in predicting prognostic outcomes. Although gastrointestinal cancer surgery is generally believed to cause weight loss or fat loss, the total amounts of adipose tissue and subcutaneous tissue increased after surgery in all stages.

In most of the previous papers (2,6) on obesity and CRC prognosis, obesity has been determined by BMI, which is a function of both body weight and height. The total amount of adipose tissue in the body, including both visceral and subcutaneous, is included in the body weight. Nevertheless, the distributions and clinical functions of these two types of fat are quite different from one another, and this discrepancy is not considered in calculating BMI alone. The proportions, absolute amounts and responses to nutritional change of these two types of fat are influenced by sex and others factors. For example, visceral obesi-

### Table 3. Multivariate Cox proportional hazard model for disease free survival and metastasis free survival

| Category                  | Disease free survival | Metastasis free survival |
|---------------------------|-----------------------|--------------------------|
|                           | Hazard ratio (95% CI) | \( P \) value            | Hazard ratio (95% CI) | \( P \) value            |
| Sex                       |                       |                          |                       |                          |
| Female                    | 1                     | 0.469                    | 1                     | 0.774                    |
| Male                      | 0.856 (0.563-1.303)   | 0.935 (0.593-1.476)      |                         |                          |
| Age                       |                       |                          |                       |                          |
| < 65 yr                   | 1                     | 0.433                    | 1                     | 0.789                    |
| \( \geq 65 \) yr          | 1.176 (0.784-1.765)   | 1.065 (0.672-1.688)      |                       |                          |
| Overall stage             |                       | < 0.001                  |                       | < 0.001                  |
| Stage I                   | 1                     | 0.510 (0.207-1.256)      | 1.153 (0.382-3.479)    | 4.001 (1.366-11.716)     |
| Stage II                  | 1.551 (1.142-3.708)   | 1.528 (0.288-0.971)      |                         |                          |
| Differentiation           |                       | 0.035                    | 0.219                  |                          |
| Well                      | 2.935 (0.913-9.434)   | 3.122 (0.749-13.016)     |                         |                          |
| Poor                      | 8.517 (1.782-40.721)  | 6.976 (1.096-44.384)     |                         |                          |
| Mucinous                  | 5.057 (1.224-20.900)  | 3.963 (0.700-22.426)     |                         |                          |
| Venous invasion           |                       | 0.026                    | 0.035                  |                          |
| Negative                  | 2.018 (1.206-3.375)   | 1.845 (1.045-3.255)      |                         |                          |
| Positive                  | 1                     | 1.263 (0.755-2.113)      |                         |                          |
| By preoperative VAT       |                       | 0.392                    | 0.375                  |                          |
| Not obese                 | 1                     | 1.225 (0.770-1.950)      | 1.263 (0.755-2.113)    |                          |
| Obese                     | 0.598 (0.375-1.052)   | 0.638 (0.382-1.063)      |                         |                          |
| By preoperative SAT       |                       | 0.065                    | 0.085                  |                          |
| Not obese                 | 1                     | 1.225 (0.770-1.950)      | 1.263 (0.755-2.113)    |                          |
| Obese                     | 0.598 (0.375-1.052)   | 0.638 (0.382-1.063)      |                         |                          |
| VAT change                |                       | 0.021                    | 0.047                  |                          |
| Decrease                  | 1                     | 0.602 (0.391-0.927)      | 0.652 (0.373-0.906)    |                          |
| Increase                  | 1                     | 1.669 (0.426-1.049)      | 0.698 (0.431-1.131)    |                          |
| SAT change                |                       | 0.080                    | 0.145                  |                          |
| Decrease                  | 1                     | 0.669 (0.426-1.049)      | 0.698 (0.431-1.131)    |                          |
| Increase                  | 1                     | 1.192 (0.735-1.934)      | 1.000 (0.581-1.721)    |                          |
| By preoperative BMI       |                       | 0.477                    | 0.999                  |                          |
| Not obese                 | 1                     | 1.732 (0.818-3.668)      | 1.160 (0.532-2.529)    |                          |
| Obese                     | 1.192 (0.735-1.934)   | 1.000 (0.581-1.721)      |                         |                          |
| Adjuvant chemotherapy     |                       | 0.152                    | 0.708                  |                          |
| Not done                  | 1                     | 1.732 (0.818-3.668)      | 1.160 (0.532-2.529)    |                          |
| Done                      | 1                     | 1.732 (0.818-3.668)      | 1.160 (0.532-2.529)    |                          |

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; BMI, body mass index.
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AUTHOR CONTRIBUTION

Research conception and design: Choe EK, Park PJ, Moon SH. Data acquisition: Choe EK, Park PJ, Ryoo SB, Oh HK, Han EC. Data analysis and interpretation: Choe EK, Park PJ, Moon SH. Statistical analysis: Choe EK. Drafting of the manuscript: Choe EK, Park PJ. Critical revision of the manuscript: Choe EK, Park PJ, Moon SH. Approval of final manuscript: all authors.

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