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Original article

Impact of subcutaneous and visceral fat adiposity in patients with colorectal cancer

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SUMMARY

Background: Although different body composition including fat adiposity has known to be associated with survival in patients with colorectal cancer (CRC), the clinical significance was inconsistent. We investigated prognostic impact of visceral and subcutaneous fat adiposity in patients with CRC after surgical resection.

Material and methods: This retrospective single center study included 987 stage I–III CRC patients (583 males, and 404 females) who underwent surgical resection between March 2005 and April 2014. Pre-operative diagnostic computed tomography images were used to quantify visceral fat area (VFA) and subcutaneous fat area (SFA). The sex-specific optimal cut-off value for body fat composition was defined using the X-tile program. The Cox proportional hazards model was used to determine the correlation fat composition and disease-free survival (DFS). Harrell's concordance index (C-index) and integrated area under curve (iAUC) were used to evaluate the predictive ability of cut-derived stratification.

Results: In univariate analysis, high SFA ($\geq$141.73 cm^2 in males and $\geq$168.71 cm^2 in females) and high VFA ($\geq$174.38 cm^2 in male and $\geq$83.65 cm^2 in female) were identified as significant prognostic factors for better DFS ($p = .001$ and $p = .003$ respectively). However, multivariate analysis revealed that high SFA independently predicted longer DFS (HR 0.505; 95% CI 0.266–0.957; $p = .036$) whereas, high VFA did not (HR 0.656; 95% CI 0.402–1.071; $p = .092$). Combining stage and SFA-cutoff showed better discriminatory performance than the model using stage solitary with respect to C-index (0.667; 95% CI 0.623–6.711; $p = .0098$) and iAUC (0.601; 95% CI 0.556–0.620).

Conclusion: High SFA was correlated with better DFS in patients with CRC. Subcutaneous fat can have additive predictive capability when incorporated into clinical decision-making

1. Introduction

Obesity is a known risk factor for several cancers, including colorectal cancer (CRC) [1]. Moreover, obesity has been shown to be an important prognostic factor in CRC, as it has been revealed that obesity is correlated with surgical and oncological outcomes [2]. Previous studies have shown an association between mortality and obesity using body mass index (BMI) as an indicator [3,4]. However, BMI cannot accurately reflect body composition, which cannot distinguish between lean and fat masses. Alternatively, computed

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tomography (CT) can be used to quantify body composition, such as muscle mass, visceral fat, and subcutaneous fat. CT images are obtained during clinical practice at diagnosis and after treatment in patients with cancer, which implies that body composition data using CT can be used as a prognostic biomarker in clinical settings.

Visceral fat is known to produce proinflammatory cytokines such as tumor necrosis factor and interleukin-6, which participate in both the initiation and progression of cancer [5,6]. Unlike visceral fat, subcutaneous fat is considered a low-grade inflammatory condition and is associated with a favorable metabolic profile of glucose and lipids [7,8]. Previous studies have suggested an association between subcutaneous fat and mortality, although there are no consistent results [9–11]. Ebadi et al. reported that lower subcutaneous fat was associated with increased mortality and shorter survival in patients with cancer originating from gastrointestinal, respiratory, renal cell carcinoma, and CRC [9]. However, the impact of subcutaneous fat showed different outcomes in patients with CRC [10,11]. Although the reason for inconsistent results has not been clearly elucidated, the different cut-off values across studies and diverse characteristics of the patients involved in the experiment might affect clinical outcomes.

Meanwhile, most previous studies have investigated the association of visceral and subcutaneous fat with mortality in European and American populations. Considering the difference in body composition between Western and Asian persons [12], this might limit the generalizability of the previous classification to other populations such as Asians. However, evidence supporting this is scarce, and little is known about the optimal cut-off of visceral and subcutaneous fat and its correlation with recurrence in Asian patients with CRC.

Thus, our study aimed to investigate the clinical impact of visceral and subcutaneous fat in predicting the survival of patients with CRC. To assess this relationship, we determined the optimal cut-off value of body fat composition in males and females, respectively.

2. Methods

2.1. Patients

This study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine (Seoul, Republic of Korea). The need for informed consent was waived in this retrospective study. Patients diagnosed with stage I–III CRC, who underwent surgical resection between March 2005 and April 2014, were initially selected.

We only selected patients who had height and body fat composition data, including visceral and subcutaneous fat. Patients with gastrointestinal stromal tumor, neuroendocrine cell tumor, hereditary CRC, inflammatory bowel disease, diagnosis with other primary cancers, synchronous CRC, and tumor lesions in the appendix or anus were excluded from the study. Further, patients without abdominal CT images within 31 days of surgery were excluded. Finally, a total of 987 patients participated in this study. Details of the inclusion criteria are presented in Supplementary Fig. 1.

2.2. Clinical variables

We obtained data on relevant covariates, including sex, age, BMI, carcinoembryonic antigen (CEA), tumor location, tumor size, complications, histologic grade, lymphovascular invasion (LVI), retrieved lymph nodes, cancer stage, and chemotherapy history from medical records. Height (m) and weight (kg) were measured at the time of diagnosis. BMI was calculated as weight divided by height squared (kg/m^2).

2.3. Follow-up protocol

Patients visited the outpatient clinic every 3 months for the first 3 years after surgery and were followed up for 3–6 months for the next 2 years. Complete blood count and routine chemistry, including serum CEA levels, were conducted during the follow-up period. Additionally, chest and abdominopelvic CT imaging studies were performed every 6 or 12 months for 5 years according to the patient's pathological stage. Colonoscopy, pelvic magnetic resonance imaging, or 18 F-fludeoxyglucose positron emission tomography were performed according to the physician's judgment.

2.4. Measurement of subcutaneous and visceral fat area

Subcutaneous fat area (SFA) and visceral fat area (VFA) were measured by analyzing CT images at the level of the third lumbar vertebrae with an open-source program named “BMI_CT” (https://sourceforge.net/projects/muscle-fat-area-measurement) within 31 days of the surgery for CRC [13]. We quantified the cross-sectional areas of SFA and VFA (cm^2) using standard Hounsfield units (HUs). According to previous research results [14,15], we considered a threshold of −190 to −30 HU as subcutaneous fat and −150 to −50 HU as visceral fat. Total fat area (TFA) was determined as the sum of the SFA and VFA. To calculate the index (cm^2/m^2) for subcutaneous fat (SFI), visceral fat (VFI), and total fat (TFI), cross-sectional areas of fat were adjusted for patient height.

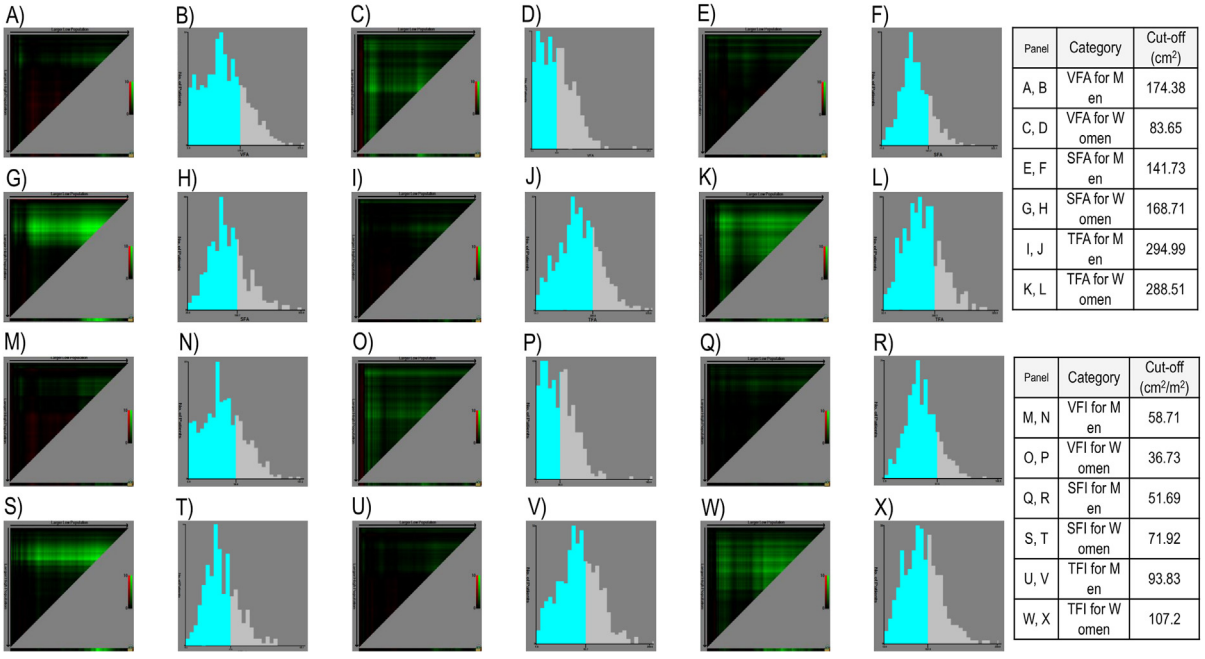
2.5. X-tile analysis for defining optimal cut-off points

We used X-tile analysis (X-tile software, version 3.6.1; Yale University School of Medicine; New Haven, CT, USA) for establishing cut-off points of fat-related parameters. Patients were split into a matched training and validation set in this program. Right-triangular gird was represented graphically with pixels representing the data from a given set of divisions. The Y-axis means all possible “high” populations, and size increases from top to bottom. The X-axis means all possible “low” population, and size increases from left to right. The program calculated χ^2value for every possible division on the grid using a color code. Red color represents inverse association and green color represents direct association showing strength of the association of each division. Optimal cut-off point was selected with the maximum χ^2 value, which appears as the brightest pixel in the grid. Statistical significance was assessed using a standard log-rank test, with P-value for each division.

2.6. Statistical analyses

Clinicopathological characteristics were analyzed using a variance test where appropriate. The Pearson chi-square test or Fisher's exact test was used to compare categorical variables. Continuous variables were analyzed using Student's t-test or the Mann–Whitney U test.

The primary outcome of the study was disease-free survival (DFS), which was defined as the time from the date of surgery to the date of detection of recurrence or any cause of death or the last follow-up date. Patients were censored and still alive at the last follow-up date. Kaplan–Meier survival curves were plotted and compared using the log-rank test. Cox proportional hazards models were used to test whether adiposity influences DFS. Variables with $p < .05$ in the univariate analysis were entered into the multivariate analysis. The results were reported using hazard ratios (HRs) and corresponding 95% confidence intervals (CIs).



Panel	Category	Cut-off (cm^2)
A, B	VFA for Men	174.38
C, D	VFA for Women	83.65
E, F	SFA for Men	141.73
G, H	SFA for Women	168.71
I, J	TFA for Men	294.99
K, L	TFA for Women	288.51

Panel	Category	Cut-off (cm^2/m^2)
M, N	VFI for Men	58.71
O, P	VFI for Women	36.73
Q, R	SFI for Men	51.69
S, T	SFI for Women	71.92
U, V	TFI for Men	93.83
W, X	TFI for Women	107.2

Fig. 1. Optimal cut-off values based on disease-free survival. X-tile analysis demonstrating the optimal cut-off values of fat related parameters based on disease-free survival. The optimal cut-off values were as follows; VFA, 174.38 cm^2 for men (A, B) and 83.65 cm^2 for women (C, D); SFA, 141.73 cm^2 for men (E, F) and 168.71 cm^2 for women (G, H); TFA, 294.99 cm^2 for men (I, J) and 288.51 cm^2 for women (K, L); VFI, 58.71 cm^2 m^{-2} for men (M, N) and 36.73 cm^2 m^{-2} for women (O, P); SFI, 51.69 cm^2 m^{-2} for men (Q, R) and 71.92 cm^2 m^{-2} for women (S, T); TFI, 93.83 cm^2 m^{-2} for men (U, V) and 107.2 cm^2 m^{-2} for women (W, X) respectively.

Table 1
Patient characteristics according to the low and high adiposity.

Variables	Categorization	VFA		*p*	SFA		*p*
		Low (n = 671)	High (n = 316)		Low (n = 765)	High (n = 222)	
		n (%)	n (%)		n (%)	n (%)	
Sex	Female	217 (32.3)	187 (59.2)		291 (38)	113 (50.9)	
	Male	454 (67.7)	129 (40.8)	<0.001	474 (62)	109 (49.1)	0.001
Age (years)	<65	398 (59.3)	136 (43)		409 (53.5)	125 (56.3)	
	≥65	273 (40.7)	180 (57)	<0.001	356 (46.5)	97 (43.7)	0.502
BMI (kg/m^2)	<25	561 (83.6)	134 (42.4)		620 (81)	75 (33.8)	
	≥25	110 (16.4)	182 (57.6)	<0.001	145 (19)	147 (66.2)	<0.001
CEA (ng/mL)	<5	466 (69.4)	214 (67.7)		526 (68.8)	154 (69.4)	
	≥5	168 (25)	93 (29.4)		202 (26.4)	59 (26.6)	
	Unknown	37 (5.5)	9 (2.8)	0.085	37 (4.8)	9 (4.1)	0.888
Tumor location	Rt. Colon	169 (25.2)	87 (27.5)		209 (27.3)	47 (21.2)	
	Lt. Colon	293 (43.7)	143 (45.3)		330 (43.1)	106 (47.7)	
	Rectum	209 (31.1)	86 (27.2)	0.430	226 (29.5)	69 (31.1)	0.176
Tumor size	<5	405 (60.4)	207 (65.5)		458 (59.9)	154 (69.4)	
	≥5	266 (39.6)	109 (34.5)	0.138	307 (40.1)	68 (30.6)	0.013
Complications	No	514 (76.6)	254 (80.4)		594 (77.6)	174 (78.4)	
	Yes	157 (23.4)	62 (19.6)	0.211	171 (22.4)	48 (21.6)	0.889
Histologic grade	G1	97 (14.5)	43 (13.6)		101 (13.2)	39 (17.6)	
	G2	521 (77.6)	248 (78.5)		599 (78.3)	170 (76.6)	
	G3 & MC & SRC	53 (7.9)	25 (7.9)	0.938	65 (8.5)	13 (5.9)	0.143
LVI	Absent	465 (69.3)	227 (71.8)		531 (69.4)	161 (72.5)	
	Present	141 (21)	58 (18.4)		159 (20.8)	40 (18)	
	Unknown	65 (9.7)	31 (9.8)	0.621	75 (9.8)	21 (9.5)	0.634
Stage	I	172 (25.6)	78 (24.7)		179 (23.4)	71 (32)	
	II	215 (32)	117 (37)		258 (33.7)	74 (33.3)	
	III	284 (42.3)	121 (38.3)	0.284	328 (42.9)	77 (34.7)	0.020
Chemotherapy	No	263 (39.2)	133 (42.1)		290 (37.9)	106 (47.7)	
	Yes	408 (60.8)	183 (57.9)	0.426	475 (62.1)	116 (52.3)	0.011

BMI: Body mass index, CEA: Carcinoembryonic antigen, MC: Mucinous adenocarcinoma, SRC: Signet-ring cell, LVI: Lymphovascular invasion, LN: Lymph node.

Additionally, Harrell's concordance index (C-index) was used to confirm the predictive power of adiposity for DFS. We compared a model using stage and different models combining stage and adiposity to evaluate the incremental benefit of adiposity in predicting prognosis. The integrated area under curve (iAUC) is an efficient statistical model to evaluate the predictive ability of prognostic factors at certain time points.

The restricted cubic spline (RCS) is a statistically suitable model when the relationship between an outcome variable and the explanatory variable shows non-linearity [16], and we used the RCS model to show the pattern of DFS according to adiposity in both males and females. Covariate variables in the RCS models were identical in multivariate analysis.

All analyses were performed using R version 3.6.3 (R-project, Institute for Statistics and Mathematics, Vienna, Austria). Statistical significance was set at $p < .05$.

3. Results

The distribution of body fat composition in the patients is shown in Supplementary Fig. 2. Visceral fat tended to accumulate more in females, whereas subcutaneous fat accumulated more in males. We defined the cut-off values of fat related parameters based on disease-free survival using X-tile program (Fig. 1). In males, VFA $\geq$174.38 cm^2, SFA $\geq$141.73 cm^2, and TFA $\geq$294.99 cm^2 were defined as high fat area. In females, VFA $\geq$83.65 cm^2, SFA $\geq$168.71 cm^2, and TFA $\geq$288.51 cm^2 were defined as high fat area. Cut-off values of VIF, SFI, and TFI were given in Fig. 1 as well. Based on these cut-off values, we divided the patients into low and high adiposity groups.

Patient characteristics according to low and high adiposity are shown in Table 1. Patients with high VFA were more prevalent in females and older adults. Those with high SFA were also more prevalent in females but younger than those in the lower SFA group. The large tumor size, high stage group and receiving chemotherapy group tended to have high SFA.

Fig. 2 shows the relationship between adiposity and long-term survival using the Kaplan–Meier curve. Survival was significantly better in patients with high VFA ($p = .0031$), SFA ($p = .00089$), and TFA ($p = .0029$). The survival curve using the fat index (cm^2/m^2) is shown in Supplementary Fig. 3 and showed similar trends to those measured by fat area. To examine whether fat adiposity had an independent role in postoperative prognosis, we conducted an adjusted Cox proportional hazard analysis (Table 2). In the univariate Cox regression model, BMI, CEA, histologic grade, LVI, stage, and chemotherapy were identified as significant prognostic factors for DFS. High VFA (HR 0.508; 95% CI 0.322–0.803; $p = .003$), high SFA (HR 0.377; 95% CI 0.207–0.685; $p = .001$), and high TFA (HR 0.447; 95% CI 0.260–0.770; $p = .003$) were also associated with better DFS. In the multivariate analysis, compared with the low adiposity group as reference, SFA alone showed a significant relationship with better DFS (HR 0.505; 95% CI 0.266–0.957; $p = .036$). VFA did not independently predict longer DFS in this model (HR, 0.656; 95% CI, 0.402–1.071; $p = .092$). Additionally, we calculated the HR for DFS using the fat index, which showed statistically similar results (Supplementary Table 1).

Next, we applied the RCS model to evaluate the association between DFS and body fat composition as continuous variables (Fig. 3). The solid line is the estimated hazard ratio (HR), and the 95% confidence interval (CI) is the interval where the HR of the population is likely to be included at the 95% level. A reverse U-shaped pattern was observed in VFA and SFA, regardless of sex. Although the exact starting value was different, the DFS increased when the body fat area was low. In contrast, the DFS decreased as the fat area increased in the high fat area. These results suggest a nonlinear association between body fat composition and DFS. On the RCS curve, the line of the part defined as very lower SFA and VFA looks somewhat low, but it was confirmed that the 95% confidence band was wide and the upper limit value was relatively high. We defined cut-off values of men and women's SFA into three tiers according to the DFS. The optimal cut-off points of SFA for prediction of DFS are 88.38 cm^2, 141.73 cm^2 in men, and 98.50 cm^2, 168.71 cm^2 in women respectively. Kaplan–Meier curve showed worse survival outcome in patients with the lowest SFA than

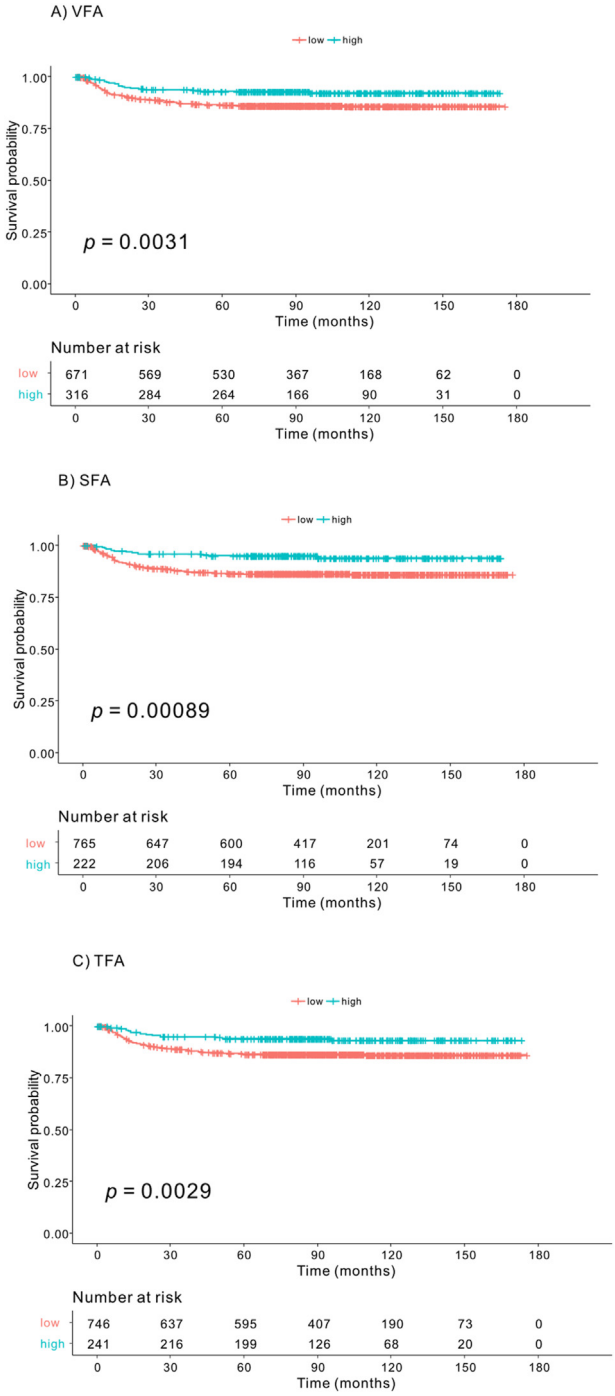


Fig. 2. Kaplan–Meier survival curve for the cumulative risk of recurrence. Kaplan–Meier survival curve showed significantly better disease-free survival in patients with higher visceral fat area ($p = .0031$) (A), subcutaneous fat area ($p = .00089$) (B), and total fat area ($p = .0029$) (C) respectively.

patients who had largest SFA in men and women respectively (Supplementary Fig. 4). With respect to VFA, we also defined cut-off values of men and women's VFA into three tiers according to the DFS. The optimal cut-off points of VFA for prediction of DFS are 122.88 cm^2, 174.38 cm^2 in men, and 24.02 cm^2, 83.65 cm^2 in women respectively. Kaplan–Meier curve showed worse survival outcome in patients with the lowest VFA than patients who had largest VFA in men and women respectively (Supplementary Fig. 5).

We evaluated the C-index to confirm the predictive power of SFA for DFS. We calculated and compared a model using the stage

Table 2
Univariate and multivariate analysis of factors associated with disease-free survival.

Variables	Categorization	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*	HR (95% CI)	*p*
Sex	Female	1			
	Male	0.878 (0.607–1.269)	0.489		
Age (years)	<65	1			
	≥65	0.849 (0.585–1.232)	0.39		
BMI (kg/m^2)	<25	1			
	≥25	0.596 (0.380–0.935)	0.024		
CEA (ng/mL)	<5	1			
	≥5	1.753 (1.193–2.575)	0.004		
	Unknown	1.093 (0.440–2.710)	0.848		
Tumor location	Rt. Colon	1			
	Lt. Colon	1.284 (0.806–2.044)	0.293		
	Rectum	1.117 (0.668–1.867)	0.673		
Complications	No	1			
	Yes	1.308 (0.858–1.993)	0.211		
Histologic grade	G1	1			
	G2	1.505 (0.803–2.819)	0.201		
	G3 & MC & SRC	3.198 (1.497–6.829)	0.002		
LVI	Absent	1		1	
	Present	2.732 (1.841–4.053)	<0.001	1.866 (1.230–2.830)	0.003
	unknown	1.586 (0.870–2.890)	0.132	1.734 (0.950–3.165)	0.070
Stage	I	1		1	
	II	2.421 (1.187–4.939)	0.015	2.351 (1.150–4.809)	0.019
	III	5.171 (2.671–10.008)	<0.001	4.220 (2.133–8.361)	<0.001
Chemotherapy	No	1			
	Yes	2.165 (1.407–3.333)	<0.001		
VFA	Low	1		1	
	High	0.508 (0.322–0.803)	0.003	0.656 (0.402–1.071)	0.092
SFA	Low	1		1	
	High	0.377 (0.207–0.685)	0.001	0.505 (0.266–0.957)	0.036
TFA	Low	1			
	High	0.447 (0.260–0.770)	0.003		

HR: Hazard Ratio; CI: Confidence Interval; BMI: Body mass index; CEA: Carcinoembryonic antigen; MC: Mucinous adenocarcinoma; SRC: Signet-ring cell; LVI: Lymphovascular invasion; VFA: Visceral fat area; SFA: Subcutaneous fat area; TFA: Total fat area.

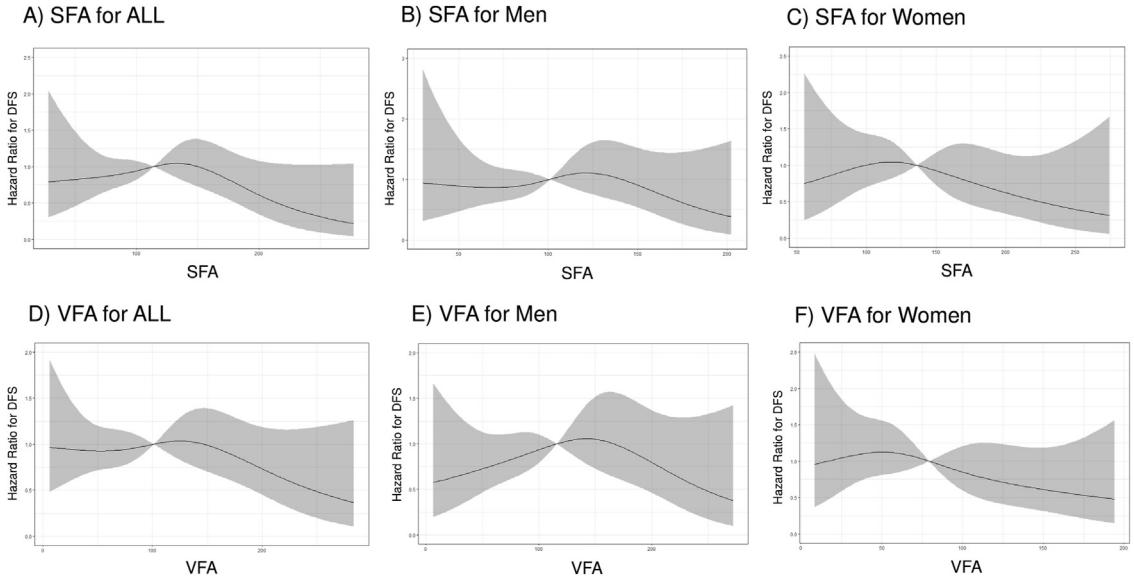


Fig. 3. Restricted Cubic Spline curve for disease-free survival using SFA and VFA. Risk of disease-free survival of SFA and VFA on the relative hazard scale in 987 patients such as SFA for all patients (A), SFA for men (B), SFA for women (C), VFA for all patients (D), VFA for men (E), and VFA for women (F). Shaded regions indicate 95% confidence bands for risk of disease-free survival as a function of SFA and VFA. Estimates are adjusted for cancer stage and lymphovascular invasion.

with the other model combining stage plus SFA-cutoff (Table 3). The C-index in the combined model was 0.667 (95% CI 0.623–0.711), which was higher than that in the solitary model (0.636, 95% CI 0.595–0.679). When we used SFI-cutoff instead of SFA-cutoff the same trend was observed (Supplementary Table 2).

To evaluate the predictive ability of subcutaneous fat as a prognostic factor during the follow-up period, we used the iAUC. The time-dependent receiver operating characteristic curve of the combined model (stage plus SFA-cutoff) was superior to that of the stage (bootstrap iAUC mean difference = 0.013; 95% CI = 0.001–0.026) during the follow-up period (Fig. 4).

4. Discussion

This study demonstrated that subcutaneous adiposity was associated with survival, and in patients with CRC who underwent curative resection, patients with higher subcutaneous fat showed better DFS. The performance of a model combining cancer stage and subcutaneous fat was better than that using the cancer stage alone in terms of iAUC and Harrell's C-index, demonstrating that subcutaneous fat could have additive predictive capability when incorporated into clinical decision-making.

The association between body adiposity and mortality has been investigated in patients with cancer, although there is some controversy regarding which factor accurately affects mortality. Ebadi et al. analyzed the significance of adiposity in patients (majority of the patients were stage III or IV) with gastrointestinal, respiratory, or metastatic renal cell carcinoma. They reported that the low subcutaneous adipose tissue index (SATI) group, defined as <52.9 cm^2 m^{-2} and <51.5 cm^2 m^{-2} in males and females, respectively, showed an increased risk for mortality (HR 1.26; 95% CI 1.11–1.43, $p < .001$) and shorter survival time than the high SATI group (13.1; 95% CI 11.4–14.7 months vs. 19.3; 95% CI 17.6–21.0 months, $p < .001$). A better prognosis with higher subcutaneous fat was also demonstrated in patients with prostate cancer [17], gastric cancer [18], and esophageal cancer [19]. Meanwhile, the association between subcutaneous adiposity and survival showed some differences in patients with CRC. Brown et al. showed that SFA was associated with mortality in an L-shaped pattern ($p = .01$) in males and J-shaped pattern ($p < .001$) in females using RCS in patients with stage I–III CRC [20]. Baar et al. also showed that SFA was associated with mortality in a nonlinear way both in males and females in the RCS and demonstrated that SFA levels below the median were associated with higher mortality in either sex in patients with stage I–III CRC [11]. The discordance of the results across studies might be due to different methods of fat measurement, cut-off values, statistical methods applied, and diverse patient characteristics such as various types of cancer or staging.

The current study showed that a high SFA was associated with a lower DFS, which is consistent with the results of Ebadi et al. in that high SFA showed better prognosis in cancer patients. There are some potential explanations for how high subcutaneous fat can be related to a lower mortality rate. In patients with cancer, energy exhaustion induced by the cachectic state is more prevalent than in healthy individuals [21,22]. Previous studies showed that subcutaneous adipose tissue was metabolically stable and resistant to lipolysis than visceral adipose tissue [23,24]. Furthermore, subcutaneous adipose tissue produces leptin, which favorably affects insulin sensitivity and energy metabolism [25,26]. Insulin and insulin-like growth factor play a role as growth factors causing tumor progression and metastasis [27,28]. Thus, high subcutaneous adipose tissue may protect patients from cachectic and insulin-resistant states, which might prevent tumor recurrence.

Regarding visceral fat, the clinical significance of visceral fat with survival in patients with CRC also showed discordant results across studies. Many studies have demonstrated that visceral obesity is not associated with mortality or survival in the eastern region [29–31] and western region [4,32,33]. Meanwhile, some studies have suggested that visceral fat might be a favorable prognostic factor in patients with CRC. Park et al. showed that

Table 3
Comparison of C-index between stage versus stage plus SFA-cutoff.

Included variables	Disease-free survival	
	Stage	Stage + SFA-cutoff
C-index (95% CI) (bootstrapped)	0.636 (0.595–0.679)	0.667 (0.623–0.711)
	$p = 0.0098$	

C-index: Harrell's concordance index; CI: Confidence Interval.

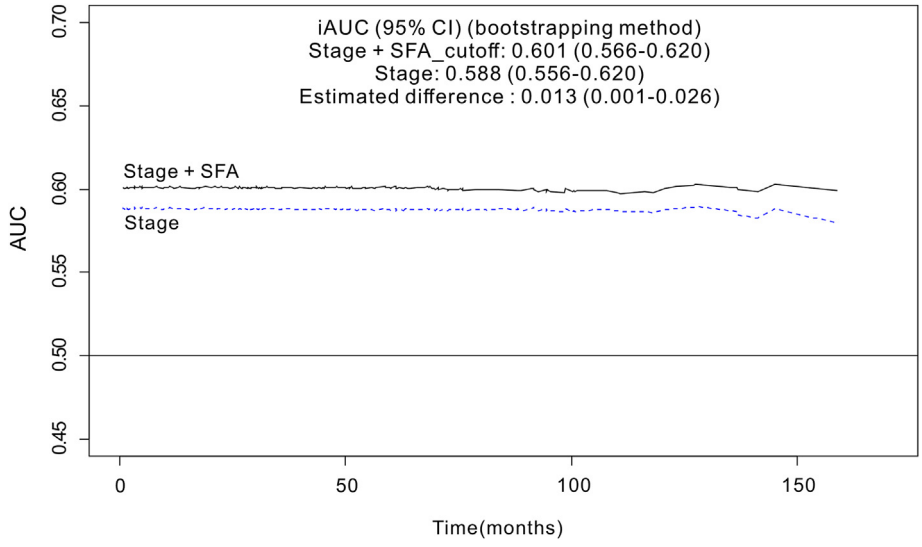


Fig. 4. Comparison of integrated area under the curve. Integrated area under the curve (iAUC) by follow-up time of stage + SFA_cutoff (black line) and stage (dotted line).

higher visceral fat, defined as >29% of VFA/TFA, was associated with better overall survival (OS) [34]. In contrast, high visceral fat showed poor OS or DFS in other studies, including patients with advanced CRC treated with chemotherapy [35,36].

Nevertheless, previous studies on this issue have some inherent limitations in interpreting the results due to the relatively small number of included patients and defining cut-off values for high visceral fat. For these reasons, a recent study investigated the overall change in HR according to visceral adiposity. In a large cohort study using RCS, visceral adipose tissue was associated with mortality in a J-shaped pattern ($p = .04$) among males and a linear pattern ($p = .08$) among females, suggesting that the prognostic effect of visceral fat may be influenced by sex or the quantity of visceral fat area [20].

Our study evaluated the RCS curve to determine the overall contribution of visceral fat to DFS. In contrast to a previous study, visceral adipose fat exhibited a reverse U-shaped association with DFS in both males and females. In addition, the cut-off value suggested as the best fit for our group showed a statistically significant protective effect of high visceral fat with recurrence in the univariate analysis in patients with non-metastatic CRC, although this was not significant in the multivariate analysis. The current study could not definitively explain why the RCS was significantly different, and the effect of visceral fat was also discordant between the studies. One possible reason may be the different ages of fat distribution across ethnicities. The visceral fat range of Western patients was 0.1–676.7 cm^2 in a previous study [20], whereas that of our study was <380 cm^2. Considering the worse survival outcome in patients with advanced CRC and a comparatively high fat range, the role of visceral fat may be dependent on ethnicity, cancer stage, and treatment. In this respect, further studies are needed to accurately determine the role of visceral fat in the prognosis.

Our study has several strengths. We measured body composition quantitatively using CT images and evaluated the association between adiposity and recurrence. Using various survival analytic methods, we demonstrated that subcutaneous fat was a more relevant prognostic factor than visceral fat or total fat. Because it is based on routinely acquired preoperative CT scans, this categorization could be widely incorporated into clinical practice at minimal cost without additional effort.

Nevertheless, our study has some limitations. 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. Body composition is dependent on ethnicity. Most Asian people, including our population, do not have an extreme fat gain. As a result, we could not evaluate the correlation between recurrence and fat composition in the higher range. Additionally, we measured body fat composition at the third lumbar vertebra. There is anatomic variation in adiposity distribution between males and females, although the third lumbar vertebra is the best compromise site for assessing adipose tissue volume [37]. Our study used CT images at a solitary point, which did not reflect longitudinal changes over the follow-up period.

In conclusion, in this large-scale study in an Asian population with stage I-III CRC, high subcutaneous fat was associated with a lower risk of DFS. Even when men and women were analyzed separately, better survival was confirmed in the group with high subcutaneous fat, respectively. However, the cut-off values were not the same due to the difference in body composition between men and women. Adding subcutaneous fat to TNM staging showed additive value in discriminating prognosis compared with TNM staging alone. Our results suggest that using CT images to quantify subcutaneous fat can be used to identify the prognosis of patients.

Conflict of interest

The authors declare that they have no competing interests. The funder has no role on study design.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.10.001.

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