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RESEARCH ARTICLE

Importance of Sex and the Distinction Between Colon and Rectal Cancer in the Association of Body Composition with Postoperative Mortality

Wouter M. Verduin M.D.,[A] Rick van den Helder M.D.[A], Thomas W.J. Janssen PhD.,[B] Alexander P.J. Houdijk M.D., Ph.D.[A]

On behalf of the INFAMUS collaborative

[A] Surgical department Northwest Clinics Alkmaar, The Netherlands
[B] Faculty of Behaviour and Movement Sciences, Vrije Universiteit Amsterdam, The Netherlands
On behalf of the INFAMUS collaborative

*Correspondence to: E-mail: a.p.j.houdijk@nwz.nl

ABSTRACT

Background: Muscle and fat influence outcome after colorectal cancer surgery. Little data exist on mortality. Muscle mass (MM) relating to lower mortality is mostly studied in dichotomous approaches as sarcopenia or skeletal muscle index (SMI) but rarely as a continuous variable. For fat, compartments as visceral, subcutaneous, or intramuscular have different metabolic impact but on mortality little is known. Sex dictates muscle and fat mass that also may differ between colon and rectal cancer patients.

Objective: To study associations of muscle and fat parameters as continuous variables with mortality in men and women after colon or rectal cancer resection.

Design: Retrospective multicenter cohort study

Setting: This study used data of the Dutch Surgical Colorectal Audit from 2011 through 2014 from 8 Dutch teaching hospitals. Body composition was assessed on pre-operative CT scans.

Patients: 2597 colon and 931 rectal cancer patients

Main outcome measures: Associations of muscle and fat measures with 5- year MR in male and female colon and rectal cancer patients.

Results: Negative associations of MM and SMI and positive associations of muscle fat (MF) and sarcopenia with mortality were found only in male patients. The effect of MM and sarcopenia was found in both colon and rectal patients whereas SMI had no effect in rectal patients. Muscle fat associated with higher mortality only in male colon patients. The only effect of visceral fat was seen in male rectal cancer patients associating with lower mortality.

Limitations: The retrospective nature of the study

Conclusion: The male predominance and differences between colon and rectal cancer patients for associations of muscle and fat parameters with colorectal cancer mortality stress the importance of separating males from females and colon from rectal cancer patients in the analysis of body composition effects on mortality.

Introduction

Body composition is associated with complications after colorectal cancer surgery but little is known about long term effects.[1–3] The preoperative abdominal CT scan for cancer dissemination enables the assessment of visceral fat- (VF), subcutaneous- fat (SF), muscle fat (MF) and muscle mass (MM). These tissues are of interest because they display different (patho)biological characteristics that may influence outcome.[4,5] Importantly, large sex differences in quantity of these tissues with more VF and MM in men and more SF and MF in women.

Too much VF or visceral obesity (VO) induces a chronic inflammatory state promoting diseases like type 2 diabetes, hypertension, cardiovascular disease, and cancer.[6,7] The cut off value for VF above which the risk of disease increases is similar for men and women.[8,9] In colorectal cancer, VO is common and the associated sex corrected risk for postoperative complications like anastomotic leakage is increased.[10] On the other hand, the large SF depot contributes less to chronic inflammation and has no clear negative metabolic effects and may even offer a survival benefit. [11,12] Accumulation of fat in muscle tissue is a sign of metabolic disturbance related to insulin resistance and the metabolic syndrome. [13,14]

Muscle mass is associated with the more positive side of the health-disease spectrum, with higher values associated with better survival after resection of a variety of gastrointestinal cancers.[15–17] In most studies, the effects of MM are analyzed in a dichotomized manner like sarcopenia or skeletal muscle index (SMI mm/m^2) with different cut points for males and females.[16,17]

The reason for dichotomizing the amount of a tissue or dividing it by the square of body length is unclear and may obscure the real association with outcome. Furthermore, because MM and the fat depots have metabolic interaction, the associations of these tissues with outcome should be studied in combination with proper correction for the influence of confounding and effect modifying variables. This is of importance because the amount of fat and muscle as assessed on the preoperative abdominal CT scan represents nothing more than a snapshot of many years of an individual's unknown and changing metabolic state. Together with the specific sex differences in body composition this stresses the importance of analyzing body composition parameters as continuous variables.

There is a surprising lack of studies that present data on associations with long term outcome for all these body composition parameters together and in a sex differentiated manner. One of the main reasons for this is the difficulty of acquiring data sets large enough for the required statistical analysis. To achieve this, we assessed body composition and combined the clinical and outcome data of colorectal cancer patients from 8 teaching hospitals over a period of 4 years.

The main purpose of this study was to assess the association of the different body composition parameters as continuous variables with 5-year overall mortality rate (MR) and recurrence rate of disease in men and women after surgery for colon and rectal cancer. The associations found were rigorously corrected for possible confounding factors and effect modification. We hypothesized that VF and MF were associated with an increase and MM with a decrease in mortality and recurrence of disease both in men and women after colon and rectal cancer resection.

Material & Methods

Setting and study design. This retrospective multicentre cohort study used data from eight Dutch hospitals; the NorthWest Clinics Alkmaar, Meander Medical Centre, Westfries Gasthuis, Kennemer Gasthuis, Spaarne Medical Center, Zaans Medical Centre, Red Cross Hospital Beverwijk, and Slotervaart Hospital. All patients who underwent colorectal cancer surgery in the years 2011 through 2014 were included. Exclusion criteria were missing relevant clinical data, missing scan data or surgery dates or loss to follow up.

Clinical data on comorbidity, disease-specific details, diagnostics, treatment, and outcome related variables were prospectively registered in the Dutch Surgical Colorectal Audit (DSCA). The dataset of the DSCA has a high level of completeness and case-ascertainment of approximately 95% in comparison to the Netherlands Cancer Registry.[18] This study was approved by the medical ethics board of the Vrije Universiteit Medical Centre in Amsterdam under number FWA00017598.

Measurement of body composition. The routine preoperative CT scan was used for body composition analysis and for rectal cancer patients, they were performed before any radio and or chemotherapy had started. Scans were retrieved, anonymised, and encoded by local software programs and assigned clinical study numbers before transporting the data for analysis. Measurements of VF, SF, MF and MM were taken at the level of the discus L3-L4 conform consensus in literature because of their strong association with total volumes.[19] (Fig 1). Hounsfield units (HU) were used to determine fatty tissues using HU ranging from -140 to -50 and -29 to 150 for muscle mass and analysed using Tomovisions SliceOmatic version 5r6b.[10] To allow comparing with common literature, the SMI and sarcopenia were defined. The SMI was

calculated by dividing MM by height in square meters and sarcopenia was defined as MM < 110 cm^2 for women and < 170 cm^2 for men.[20] Body composition analysis was performed by two physicians (WMV and RvdH) with an interobserver correlation of 92.

Patient characteristics and outcome variables. Patient characteristics were age, body mass, height, sex, location of the tumor, Tumor Node Metastasis (TNM) stage, radicalness of resection, double tumor, recurrence, and location of recurrence of disease. The Charlson comorbidity index (CCI) was calculated as described in the original article by Charlson and colleagues.[21] The primary endpoint was overall survival calculated as days after the surgery. All other patient characteristics were tested for as confounder.

Statistical analysis. Differences in patient characteristics were analysed using chi-square testing in case of nominal or ordinal variables, independent samples t-test in case of normally distributed continuous variables and Wilcoxon signed rank test for non-normally distributed variables. Cox regression analysis was performed for the association of each of the body composition compartments with survival. Multivariate analysis was adjusted for confounding factors and effect modification. Variables tested for confounding effects were the remaining body compartments, sex, age, CCI, TNM stadium, radicalness of resection and double tumors. Confounding factors were selected in a forward selection procedure with a limit of 5% change in effect size using a basic cox regression model with only one body compartment as independent variable and either disease-free or overall survival as dependent variable. The confounder with the largest change in effect size (at least 5%) was included in the new model. The selection procedure was repeated using the remaining covariables. The procedure was stopped after none of the covariables changed the effect size by more than 5% or after reaching the maximum number of confounders defined as 10% of the total events. Selected confounders were tested for effect modification by adding an interaction term to the analysis. When the interacting term was significant ($p<0.05$) interacting was deemed significant. Body composition was analysed per 10cm^2 to enhance interpretability.

The analysis was performed using the Statistical Package for the Social Sciences version 20.0. A p-value of <0.05 was considered statistically significant.

Table 1: Patient characteristics

	Overall group (N=3 528)	**Colon cancer (N=2 597)**	**Rectal cancer (N=931)**	**P-value**
Age (mean, SD)	70.2 (10.8)	71.0 (10.7)	68.1 (10.7)	.000
Male gender (N, %)	1 904 (54.0)	1 338 (51.5)	566 (60.8)	
VF (mean, SD)	157.8 (94.9)	156.7 (95.2)	160.9 (94.0)	.246
SF (mean, SD)	179.0 (81.8)	178.1 (82.4)	181.6 (80.0)	.295
MM (mean, SD)	134.6 (32.7)	132.0 (32.0)	141.7 (33.5)	.000
MF (median, IQR)	2.51 (1.11-4.81)	2.71 (1.22-5.07)	2.01 (0.91-4.10)	.000
SMI (mean, SD)	45.0 (8.7)	44.3 (8.5)	46.8 (9.0)	.000
Sarcopenia (N, %)	2 267 (64.3)	1 713 (66.0)	554 (59.5)	.000
Body Mass Index (mean, SD)	25.7 (4.0)	25.7 (4.1)	25.9 (4.0)	.292
CCI (median, IQR)	3 (2-4)	3 (2-5)	3 (2-4)	.000
TNM stadium				
0 (N, %)	65 (1.8)	2 (0.1)	63 (6.8%)	.000
I (N, %)	717 (20.3)	433 (16.7)	284 (30.5)	.000
II (N, %)	1 162 (32.9)	935 (36.0)	227 (24.4)	.000
III (N, %)	1 065 (30.2)	800 (30.8)	265 (28.5)	.000
IV (N, %)	519 (14.7)	427 (16.4)	92 (9.9)	.000
Radicalness				
R0	3 428 (97.2)	2 522 (97.1)	906 (97.3)	.059
R1	74 (2.1)	51 (2.0)	23 (2.5)	.059
R2	26 (0.7)	24 (0.9)	2 (0.2)	.059
Five year Mortality (N, %)	1211 (34.3)	909 (35.0)	302 (32.5)	.000
Multiple tumours (N, %)	143 (4.1)	104 (4.0)	39 (4.2)	.395
Recurrence of disease (N, %)	1164 (33.0)	882 (34.0)	297 (32.0)	.001

Differences between the colon and rectal cancer group are shown.

Results

Patient characteristics.

From 2011 through 2014, 2597 patients underwent a colon cancer and 931 rectal cancer patients. In Table 1 the differences in characteristics between these two groups are displayed. Rectal cancer patients were younger, had more MM, less MF, higher SMI, lower percentage sarcopenia (all P=0.000). TNM differed with more 0 and I and less III and IV stages in rectal cancer patients. A total of 909 (35.0 %) colon patients died within 5 years. For rectal cancer patients this was 302 (32.5%). All patient characteristics are summarized in table 1.

Sex differences are shown for the body composition measures. Because sarcopenia and SMI have different sex related cut off points these results are shown. In the colon cancer group, more men than women had sarcopenia (982, 73.4 % vs 731, 58.1%; p=0.000) this was also found for the rectal group (364, 64.3% vs 190, 52.1%). For SMI in the colon group the index was lower in males than females (1321, 51.6% vs 556, 60.6%: p=0.000).

Table 2: 5-year mortality and body composition in colorectal carcinoma

	Colorectal group (N=3528)		**Colon cancer (N=2597)**		**Rectal cancer (N=931)**	
	Odds-ratio	P	Odds-ratio	P	Odds-ratio	P
Total						
VF	1.000 (.991-1.010)[1]	.952	1.007 (.996-1.018)[7]	.218	.977 (.956-.998)[13]	.029
SF	1.002 (.991-1.013)[2]	.760	.997 (.984-1.009)[8]	.601	1.023 (.999-1.048)[14]	.057
MM	.944 (.910-.980)[3]	.002	.948 (.909-.988)[9]	.012	.921 (.851-.996)[15]	.039
MF	1.030 (1.010-1.050)[4]	.003	1.036 (1.013-1.059)[10]	.002	1.004 (.962-1.049)[16]	.850
SMI	0.982 (.972-.993)[5]	.001	.983 (.971-.995)[11]	.005	.981 (.959-.1.003)[17]	.092
Sarcopenia	1.321 (1.111-1.569)[6]	.002	1.214 (.999-1.475)[12]	.052	1.858 (1.295-2.666)[18]	.001
Male						
VF	1.003 (.991-1.014)[19]	.632	1.012 (.999-1.025)[25]	.082	.977 (.953-1.002)[31]	.073
SF	.991 (.974-1.009)[20]	.309	.983 (.963-1.004)[26]	.107	1.017 (.984-1.051)[32]	.311
MM	.926 (.885-.968)[21]	.001	.927 (.881-.976)[27]	.004	.909 (.837-.987)[33]	.024
MF	1.032 (1.005-1.060)[22]	.022	1.041 (1.011-1.072)[28]	.008	1.009 (.943-1.078)[34]	.801
SMI	.978 (.965-.991)[23]	.001	.972 (.957-.988)[29]	.001	.982 (.955-.1.009)[35]	.193
Sarcopenia	1.443 (1.124-1.853)[24]	.004	1.333 (.991-1.792)[30]	.057	2.166 (1.281-3.661)[36]	.004
Female						
VF	.999 (.981-1.017)[37]	.910	1.002 (.983-1.022)[43]	.814	.977 (.935-1.020)[49]	.292
SF	1.006 (.991-1.021)[38]	.431	1.002 (.986-1.019)[44]	.776	1.027 (.991-1.064)[50]	.145
MM	.997 (.932-1.067)[39]	.935	1.012 (.940-1.089)[45]	.751	.918 (.776-1.087)[51]	.321
MF	1.025 (.995-1.056)[40]	.098	1.031 (.997-1.066)[46]	.075	.993 (.931-1.058)[52]	.822
SMI	.998 (.981-.1.016)[41]	.836	1.004 (.984-1.023)[47]	.712	.973 (.931-1.016)[53]	.213
Sarcopenia	1.171 (.922-1.487)[42]	.196	1.112 (.854-1.449)[48]	.431	1.445 (.795-2.628)[54]	.228

Hazard ratios and range for body composition on 5-year mortality rate. Confounding of: [1] MM, CCI, TNM, MF, SF, sex, age, radicalness of resection and double tumors. [2] MF, age, TNM, sex, MM, VF, CCI, radicalness of resection and double tumor. [3] age, sex, TNM, VF, MF and CCI. [4] CCI, TNM, age and SF. [5] Sex, age, TNM, VF and MF. [6] Age, TNM, sex and VF [7] MM, CCI, TNM, SF, age, sex, MF and radicalness of resection. [8] MF, age, TNM, VF, sex, MM, radicalness of resection, double tumors and CCI. [9] Sex, age, TNM, VF ,MF and CCI. [10] CCI, TNM, age and SF. [11] Age, VF, sex, TNM, MF and CCI. [12] Age, TNM, VF, radicalness of resection, sex and CCI. [13] CCI, sex, SF, TNM, MM, double tumors and age. [14] MF, CCI, VF, sex, MM and double tumor. [15] Sex, CCI, TNM, SF, VF, age and radicalness of resection. [16] CCI, sex, VF, TNM, MM, SF, age and radicalness of resection. [17] Sex, age, VF, radicalness of resection, TNM, MF, CCI and SF. [18] CCI, TNM and SF. [19] MF, CCI, MM, TNM, SF, radicalness of resection, double tumor and age. [20] MF, MM, age, TNM, VF, radicalness of resection and double tumor. [21] MF, age, radicalness of resection, CCI, TNM and VF. [22] CCI, SF, MM and radicalness of resection. [23] age, radicalness of resection, CCI, TNM, VF and MF. [24] Age and radicalness of resection. [25]

MF, SF, CCI, MM, radicalness of resection, TNM and age. [26] MF, MM, VF, age, TNM and radicalness of resection. [27] MF, age, VF, CCI, TNM and SF. [28] CCI, SF, MM and TNM. [29] Age, CCI, SF, MF, VF and TNM. [30] Age, SF, CCI, radicalness of resection, TNM and VF. [31] MF, TNM, MM, age, double tumor, CCI and SF. [32] MM, MF, VF, CCI, TNM and radicalness of resection. [33] CCI, TNM, VF, SF and double tumor. [34] CCI, TNM, MM, VF, SF and radicalness of resection. [35] CCI, TNM, VF, MF, SF , age and radicalness of resection. [36] CCI, TNM, age and VF. [37] MF, CCI, TNM, age, SF, radicalness of resection, double tumor and MM. [38] MF, TNM, VF, age, CCI and radicalness of resection. [39] MF, age, TNM, SF, VF, CCI, double tumor and radicalness of resection. [40] age, TNM and SF. [41] Age, TNM, SF, MF, CCI, VF and radicalness of resection. [42] Age, TNM, SF, MF and radicalness of resection. [43] MF, TNM, SF, CCI, age, MM, double tumor and radicalness of resection. [44] MF, TNM, VF, age, radicalness of resection, MM, double tumor. [45] MF, age, TNM, VF, CCI, SF and double tumor. [46] TNM, age, VF and CCI. [47] Age, TNM, VF, MF, CCI, radicalness of resection, SF. [48] Age, TNM, VF, radicalness of resection, SF and MF [49] CCI, SF, age, TNM and MM. [50] MM, radicalness of resection, TNM, CCI and VF. [51] MF, age, CCI, VF, SF, radicalness of resection and TNM. [52] CCI, TNM, age, SF, MM, VF, double tumor and radicalness of resection. [53] Age, TNM, SF, radicalness of resection, VF, CCI and MF. [54] CCI, VF, age, SF, TNM and radicalness of resection

Associations with five-year mortality.

In Table 2 the associations of body composition parameters with 5-year mortality are shown for the total colorectal and separate colon and rectal cancer groups for both men and women. The Hazard ratios are presented after adjustment for their confounders that are shown in the legends.

For the total colorectal group, MM was associated with reduced mortality (OR .944: p=.002) showing a reduction of 5.6% per 10cm^2 MM. Effect modification for sex was evident (OR 1.077; p=.039) with the association only found in male patients (OR.926: p=0.001). For TNM (OR 1.069; p=.004) effect modification was found as well indicating stronger associations at higher TNM's. MF associated with an increased risk of mortality (OR 1.030: p=.003) that was explained by an association in male colorectal patients (OR 1.032: p=.022) that was statistically more evident than in females (OR 1.025: p= .098). In the total colorectal group, SMI associated with a reduced mortality risk (OR .982: p=.001) with significant effect modification for sex (OR 1.024:p=.021) and only seen in male patients (OR .978:p=0.01). Sarcopenia associated with higher MR in the colorectal group (OR 1.321: p=.002) with effect modification for age (OR 1.021: p=.012). This effect was only found in the male total colorectal group (OR 1.443: p=.004, no effect modification). Both VF and SF had no association with mortality.

Between the colon and rectal groups, similarities and differences in the association with 5-year mortality were found. In rectal cancer patients, VF was associated with lower MR and SF showed a trend for a higher MR (OR .997:p=.029 and OR 1.023:p=.057, resp.) explained more so by the association in males than in females (OR .977;p=.073 and OR .977;p=.292) MM associated with reduced MR in both the colon and rectal group (OR 0.948; p=.003 and OR .921:p=.039). Significant effect modification was found for sex (OR 0.927; p=.004 and OR .909:p=.024). This effect was found only in male patients of both groups. Muscle fat was associated with an increased MR only in colon patients (OR of 1.036: p=.002) with a more pronounced effect in males (OR 1.041:p=.008) than in females (OR 1.031: p=.075). Significant effect modification was found for the CCI (OR 0.982; p=.009) indicating a weaker association in patients with a higher CCI. The reduced MR associated with SMI in the overall colorectal group was explained by a significant effect in the colon group (OR .983: p=.005) but not in rectal cancer patients (OR .981: p=.092). Significant effect modification was found for sex (OR 1.030; p=.011) with an association found in male colon patients only (OR .972;p=0.001). The association between sarcopenia and increased mortality in the male colorectal group was stronger in the total rectal- and male rectal groups (OR 1.858: p=.001 and OR 2.166: p=.004 resp.) than in the total colon- and male colon group where it just lost significance (OR 1.333:p=0.057 and OR 1.214:p=0.052. No effect modification was found.

Recurrence of disease.

The associations of body composition with recurrence of disease are summarized in table 3. In the overall colorectal group, only in women a trend was observed for VF with a reduced risk of recurrence with an OR of .973 (p=.059). This effect was lost in the separate colon and rectal cancer group with no associations for the other body composition measures.

Table 3. Recurrence of disease and body composition in colorectal carcinoma

	Colorectal group (N=3 528)		Colon cancer (N=2 597)		Rectal cancer (N=931)	
	OR	P	OR	P	OR	P
Overall						
VF	.994 (.980-1.008)[1]	.386	.995 (.978-1.013)[7]	.586	.993 (.968-1.018)[13]	.579
SF	1.001(.986-1.017)[2]	.870	1.003 (.983-1.022)[8]	.797	.993 (.965-1.023)[14]	.651
MM	1.035 (.982-1.090)[3]	.201	1.026 (.962-1.095)[9]	.436	1.040 (.950-1.139)[15]	.393
MF	1.001 (.968-1.035)[4]	.944	1.020 (.983-1.059)[10]	.295	.945 (.880-1.015)[16]	.123
SMI	1.003 (.988-1.018)[5]	.675	.998 (.979-1.017)[11]	.841	1.009 (..983-1.036)[17]	.483
Sarcopenia	1.033 (.816-1.310)[6]	.785	1.055 (.788-1.411)[12]	.721	.991 (.654-1.503)[18]	.968
Male						
VF	1.000 (.983-1.017)[19]	.983	1.000 (.980-1.021)[25]	.965	1.000 (.971-1.029)[31]	.988
SF	.997 (.973-1.023)[20]	.842	1.000 (.970-1.031)[26]	.990	.988 (.946-1.031)[32]	.573
MM	1.039 (.975-1.107)[21]	.235	1.024 (.944-1.110)[27]	.566	1.059 (.947-1.184)[33]	.316
MF	1.006 (.958-1.055)[22]	.815	1.028 (.976-1.084)[28]	.298	.921 (.830-1.023)[34]	.124
SMI	1.008 (.990-1.027)[23]	.382	1.001 (.977-1.026)[29]	.905	1.018 (.984-1.053)[35]	.302
Sarcopenia	1.046 (.749-1.461)[24]	.792	1.184 (.768-1.827)[30]	.444	.845 (.488-1.462)[36]	.548
Female						
VF	.973 (.946-1.001)[37]	.059	.978 (.946-1.011)[43]	.185	.961 (.910-1.015)[49]	.154
SF	1.009 (.987-1.031)[38]	.435	1.008 (.983-1.034)[44]	.535	1.005 (.964-1.047)[50]	.827
MM	1.047 (.952-1.151)[39]	.346	1.048 (.937-1.173)[45]	.409	1.018 (.854-1.213)[51]	.842
MF	1.009 (.964-1.057)[40]	.697	1.025 (.971-1.081)[46]	.377	.969 (.882-1.065)[52]	.515
SMI	.998 (.973-1.024)[41]	.886	.995 (.965-1.026)[47]	.760	1.001 (.958-1.047)[53]	.951
Sarcopenia	1.007 (.717-1.413)[42]	.969	.952 (.638-1.421)[48]	.809	1.175 (.625-2.208)[54]	.617

Confounding of: [1] MF, MM, CCI, age, TNM, SF and radicalness of resection. [2] MF, TNM, sex, VF, MM, age, radicalness of resection and CCI. [3] VF, CCI, age, sex and TNM. [4] CCI, age, MM, VF, TNM, SF and sex. [5] Sex, CCI, age, TNM and VF. [6] CCI, age, sex, TNM, VF, SF and radicalness of resection. [7] MM, MF, CCI, radicalness of resection, double tumor, age, SF and sex. [8] MF, CCI, sex, age, VF, MM, double tumor and TNM. [9] MF, VF, CCI, sex, age, radicalness of resection TNM, SF. [10] CCI, age, MM, VF, SF and radicalness of resection. [11] Sex, CCI, age, SF, MF, VF, TNM, double tumor and radicalness of resection. [12] CCI, age, sex, SF, MF, VF and double tumor. [13] MF, SF, double tumor, TNM, sex, age, MM, radicalness of resection and CCI. [14] MF, age, VF, MM, sex, double tumor and radicalness of resection. [15] MF, age, sex, VF, double tumor, TNM and SF. [16] SF, age and TNM. [17] MF, age, VF, sex, double tumor and SF. [18] Age, SF, TNM, MF, sex, radicalness of resection, double tumor, CCI and VF. [19] MF, age, MM, CCI, radicalness of resection, TNM, double tumor and SF. [20] MF, VF, age, MM, CCI, double tumor and radicalness of resection. [21] age, radicalness of resection, SF, CCI and TNM. [22] age, CCI, radicalness of resection, VF, MM, SF, double tumor and TNM. [23] Age, radicalness of resection and TNM. [24] Age, radicalness of resection, TNM, VF, CCI and double tumor. [25] MF, radicalness of resection, SF, age, MM, CCI, double tumor and TNM. [26] MF, age, MM, radicalness of resection, CCI, double tumor, TNM and VF. [27] MF, age, SF, CCI and VF. [28] age, CCI, SF, radicalness of resection, double tumor and MM. [29] Age, VF, CCI, MF, SF, double tumor, radicalness of resection and TNM. [30] Age, VF, CCI and SF. [31] MF, SF, age, MM, TNM, double tumor, radicalness of resection and CCI. [32] MF, VF, age, MM, TNM and radicalness of resection. [33] MF, age, radicalness of resection, double tumor, SF and TNM. [34] age, TNM, VF, SF and double tumor. [35] Age, SF, MF, radicalness of resection, double tumor and CCI. [36] Age, TNM, SF, radicalness of resection, double tumor and MF. [37] SF, CCI and MM. [38] MF, VF, CCI, MM, TNM and age. [39] MF, VF, CCI, SF, age and TNM. [40] VF, age, SF, MM and TNM. [41] VF, age, TNM, MF, SF, radicalness of resection and double tumor. [42] Age, TNM, VF, SF, double tumor, MF, radicalness of resection and CCI. [43] MF, SF, CCI, MM and double tumor. [44] MF, VF, age, MM, double tumor and TNM. [45] MF, age, VF, SF and TNM. [46] age, VF, SF and MM. [47] Age, VF, MF, TNM, SF and radicalness of resection. [48] Age, VF, SF, TNM, double tumor and MF. [49] MF, age and SF. [50] MF, VF, TNM, CCI, age, MM and radicalness of resection. [51] MF, VF, age, double tumor, TNM, CCI, radicalness of resection and SF. [52] VF, age, TNM, SF and radicalness of resection. [53] VF, MF, age, TNM, SF, CCI, double tumor and radicalness of resection. [54] VF, MF, age and CCI.

Discussion

Our data show that sex and the separate analysis of colon and rectal cancer patients strongly influence the association of muscle and fat parameters on 5-year MR after resection. Our data also show the multitude of confounding variables involved in the multivariate analysis of colorectal cancer mortality. To judge the influence of MM and fat parameters these variables need to be corrected for.

A prominent finding was that as a continuous variable MM associated with lower MR only in males in the overall colorectal and the separate colon and rectal groups. By using the SMI van Baar et al. already witnessed a selective effect on MR in males in colorectal cancer patients but did not separate colon form rectal cancer.[17] Another study using MM as sarcopenia also found a negative effect on survival but sex differences and separate analysis were not reported.[16] Some smaller studies

reported increased mortality for sarcopenia or low SMI in colorectal patients without correcting for confounders including sex.[22–24] Here we show that low MM defined as sarcopenia increased MR again only in males both after colon and rectal cancer resections. The effect of MM whether used as a continuous variable or as sarcopenia therefore shows similar effects on MR .[25,26] An important difference with previous data was that the index SMI had no effect on MR in rectal cancer patients. An index follows different statistics and in the case of SMI the effect of MM becomes influenced by the square of body length, introducing an additional variable that may differ between groups and sex. [16,17,27] Indeed, all muscle parameters including muscle fat in the rectal group significantly differed from the colon group (Table 1). The reported U-shaped association between SMI and MR assumes a quadratic function suggesting that both extremes (e.g. high and low) of MM are associated with increased risks. This contrasts with our findings of a strong significant effect on a progressive linear scale for MM. [25,26]Our data question why SMI or sarcopenia as derived measures are in use. Without dividing MM by the square of body height, its effect size was even greater on a larger numerical range, therefore providing more detailed information.

The strong confounding influence we found for age and sex on MM effects is of recent interest. Studies have shown biological differences not only in age-related loss of MM but also type of muscle fibre expression and differences in almost 3000 muscle genes between sexes.[25,28] These differences not only relate to hormonal differences but also to functional and metabolic activity that may be better measured by functional muscle strength than MM.[25,28,29]. As a protein source muscle may sustain life and the larger amount of MM in men may contribute to the sex differences in associated MR. Why MM does not provide a survival benefit in women is unexplained and warrants further study.

Contrasting with the association of MM, MF had an increased risk of 3-year mortality only after colon resections reaching significance in men (P= .008) and a trend in women (P=.075). The effects of MF are thought to be comparable to VF and associated with a state of chronic inflammation and impaired muscle function.[30] Accumulated MF signals a metabolic derangement leading to or associated with the metabolic syndrome worsening the ability to recover increasing the risk of mortality.[31,32] On the effect of MF on MR in colorectal cancer studies report conflicting data. Okugawa et al. found no effects on mortality for MF in colorectal patients [33] while others after categorizing MF or excluding stage IV colorectal cancer did find an effect on mortality.[23,24] Looking at our data, these discrepancies may be explained by not analysing colon and rectal cancer patients as separate groups. We here show that the negative effect of MF in the overall colorectal group was explained by an effect only in the colon cancer patients. In line with the MM data this again stresses the importance of separate analysis.

Visceral fat had no effect on MR in the overall colorectal group but lowered MR in the rectal cancer group (P=0.029) an effect explainable only from the non-significant association found in men. In a small study, Rickles et al. also showed a nearly three-fold decrease in disease-free survival in 111 visceral obese patients compared to 108 non visceral obese stage II colorectal patients. [34]

However, no separate analysis for colon and rectal was done hampering proper comparison. Subcutaneous fat had a negative effect on MR only in the overall rectal cancer group (p=0.057) that could not be attributed to a sex difference. Other smaller, dichotomized studies in combined colorectal patients did not find an effect for adipose tissue.[23]

To our knowledge, we are the first to report on the differences between colon and rectal cancer for associations of body composition with survival. Our data support considerations that these states of gastrointestinal cancer represent truly different disease entities not just anatomically but also with regards to survival, metastatic patterns, embryological origin, and response to treatment.[35] Considering our findings and the differences in patient characteristics it is advised for future studies to separately analyse colon and rectal cancer patients.

No significant effects were found for body composition on the effects for recurrence of disease. For VF only a trend for reduced risk of recurrence of disease in women in the overall colorectal group was found which contradicts findings of others. Some studies reported on increased risk of recurrence of disease with a combined measure of VF with SF in specific subgroups but not women.[36,37] Other studies did not find such effects in women whereas Vledder et al. reported an increased risk of recurrence in men with central obesity.[38] These previous studies were performed with small sample sizes, often in subgroups of patients, without correction for confounders making results difficult to interpret. Even in our large data set of 1600 women the effect was short of significance questioning clinical relevance.

Our study has several strengths and limitations. Strengths are the large sample size, the use of a validated nationwide dataset and the multicentre approach with 8 large teaching hospitals. Another strength is the analysis of body composition

variables on a continuous scale, instead of dichotomizing or dividing by height, increasing statistical relevance. Evident limitations come with the drawbacks of retrospective analysis of datasets even when data are gathered prospectively. Another limitation is the use of only one preoperative CT measurement of body composition because body composition may have changed considerably with in a 3-year time frame.

Conclusions

In this study, MM as a continuous measure was strongly associated with lower overall MR in men after both colon and rectum resections, which remained present after extensive correction for confounding factors. This shows that there is no need for the use of surrogate measures such as the SMI to judge MM effects on survival. We also found strong disparities between sexes and the colon and rectum groups stressing the importance of separate analysis in future studies on body composition. We found no effect of body composition on disease recurrence. Our data are of value for prehabilitation and rehabilitation programs targeting MM in males in both colon and rectal cancer patients.

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