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Analytic Morphometric Assessment of Patients Undergoing Colectomy for Colon Cancer

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Background: Analytic morphometrics provides objective data that may better stratify risk. We investigated morphometrics and outcome among colon cancer patients.

Methods: An IRB-approved review identified 302 patients undergoing colectomy who had CT scans. These were processed to measure psoas area (PA), density (PD), subcutaneous fat (SFD), visceral fat (VF), and total body fat (TBF). Correlation with complications, recurrence, and survival were obtained by *t*-tests and linear regression models after adjusting for age and Charlson index.

Results: The best predictor of surgical complications was PD. PMH, Charlson, BMI, and age were not significant when PD was considered. SF area was the single best predictor of a wound infection. While all measures of obesity correlated with outcome, TBF was most predictive. Final multivariate Cox models for survival included age, Charlson score, nodal positivity, and TBF.

Conclusions: Analytic morphometric analysis provided objective data that stratified complications and outcome better than age, BMI, or co-morbidities.

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KEY WORDS: colon cancer; sarcopenia; obesity; colectomy; morphometric

INTRODUCTION

Obesity, as measured by body mass index (BMI) has been associated with both worse oncologic outcomes and increased morbidity of treatment among patients with colorectal cancer, although the exact reasons are unclear [1–4]. The impact of older age on colorectal cancer outcomes is also a question, as older individuals are less represented in clinical trials and may be undertreated despite evidence of a survival benefit with surgery and adjuvant chemotherapy [5]. These clinical dilemmas are even more concerning given that 40% of colorectal cancer patients in the U.S. are over 75 years of age, and obesity rates in the U.S. are rising dramatically [6,7]. However, chronologic age can be a poor measure of the relative frailty or vitality of an individual, and BMI, while a useful clinical tool, is a relatively non-specific assessment of body composition that does not directly measure adiposity. Use of these isolated values may not paint an accurate physiologic portrait of the patient.

Analytic morphometric analysis, using morphometric measures obtained from pre-treatment imaging such as core muscle size, body composition, bone mineral density, etc., provides objective data that may better stratify risk. We have previously demonstrated that such measures improve preoperative risk stratification [8,9], predict for post-operative complications [10,11], and interestingly may also predict oncologic outcome [10]. Given our previous observations, we therefore sought to determine whether analytic morphometric analysis might not only predict surgical complications among colorectal cancer patients, but also long-term outcome.

METHODS

Patients

An IRB-approved retrospective review was performed of all patients undergoing resection for colon cancer at the University of Michigan between 2000 and 2010. Of the 515 patients who were identified, 315 had CT scans of the abdomen and pelvis performed at the University of Michigan and therefore could be included in the study. Patients with extra-hepatic metastases undergoing palliative operations were excluded. The remaining 302 patients comprised the study group. Patient and tumor characteristics including age, gender, height and weight, presentation, and medical co-morbidities, as well as treatment data including type of surgery, complications, and adjuvant therapy were obtained for every patient. Recurrence and survival information was obtained from computerized medical records and from the Tumor Registry.

Analytic Morphomics

CT scans were processed using semi-automated algorithms programmed into MATLAB v13.0 as described in previous work [8,11]. These algorithms use novel, high-throughput techniques to identify the linea alba and the anterior abdominal skin along the midline at each vertebral level from T12 to L4. The average distance between the linea alba and the anterior skin along T-12 to L4 was labeled the subcutaneous fat distance (SFD), and the average distance between the anterior aspect of the vertebra and the linea alba was labeled the

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visceral anterior-to posterior (AP) distance (VF). The sum of the SFD and visceral AP distance was labeled the total AP distance, or total body fat (TBF).

Both psoas area (PA) and psoas density (PD) were determined in our study population. Cross-sectional areas of the left and right psoas muscles at the level of the fourth lumber vertebra (L4) were measured. The area of the resulting enclosed regions was then computed to generate the cross-sectional area of the psoas muscles. Fatty infiltration of the psoas muscle was assessed by measuring the density, in Hounsfield Units (HU), within these regions, with lower HU reflecting more fat infiltration [12]. This highly reproducible method correlates with muscle triglyceride content on muscle biopsy [13–15].

In order to compare morphomic measurements to a more standardized and validated morbidity index, we also calculated the Charlson co-morbidity Index for each patient [16]. The Charlson co-morbidity index is based on a weighted score assigned to each of 17 comorbidities, based on the relative risk of mortality, and has been validated in various larger populations [17–19]. The Charlson score has specifically been utilized and validated in studying the morbidity and mortality among colorectal cancer patients, including complications of colorectal cancer surgery, and is commonly used as a control in this setting [20–24].

Statistical Analysis

Patients' anthropomorphic measurements, disease characteristics, and the occurrences of complications after surgery were compared to the morphometrics using two-sample *t*- tests or analysis of variance techniques when the number of groups exceeded two. Linear regression models were used to assess the association between continuous covariates. For time-to-event endpoints disease-free and overall survival, time was calculated from the date of surgery until disease recurrence or death, or death, respectively. Patients not experiencing the endpoint of interest were censored on the date of their last known clinical follow-up. Cox proportional hazard regression models were used to assess the association with morphomic measurements, both univariately and multivariately after adjusting for significant patient characteristics such as age and co-morbidity index. For all statistical tests, *P*-values at or below 0.05 were considered significant.

RESULTS

The details of the patient population are summarized in Table I. There was no difference in mean PD between genders (53.0 for males, 54.6 for females, $P = 0.14$) while TPA was expectedly greater for males (956.2 vs. 828.7, $P < 0.0001$). Table II shows the relationship between the morphometric measurements and age, BMI, and Charlson score. Not surprisingly, BMI was significantly associated with all of the morphometric measurements. Age was significantly correlated with PD, PA, and VF. Table II also demonstrates the interactions between individual morphometrics.

There was no significant past medical history in 107 (37%) of the patients. A cardiovascular history was present in 30.4% of patients (excluding hypertension). A pulmonary history was present in 13.1%. Fifteen percent of the patients had diabetes (18 Type 1, 40 Type 2) and 22% of patients had a prior cancer history. We specifically examined the relationship between the morphometrics and both the Charlson score and specific co-morbidities. The median Charlson score was 5 (range 0–17), and was significantly associated with PD, VF, and TBD (Table II). Table III highlights the relationships between morphometrics and the co-morbidity categories. Not surprisingly, diabetes was associated with decreased PD and all the obesity measurements. Cardiac disease was also strongly associated with all the measurements except for SFD. Pulmonary disease was associated with decreased PD and increased total body area. Decreasing PD was also more common in patients who had a prior non-colorectal cancer.

TABLE I. Patient and Tumor Characteristics for Study Cohort (n = 302)

Gender	
Male	157 (52%)
Female	145 (48%)
Age	
Average	67.9 ± 12.4
Range	26 to 94
BMI	
Median	28.7 ± 8.0
Range	19 to 92.6
Charlson co-morbidity index	
0–2	24 (8%)
3–4	80 (26%)
5–7	160 (53%)
8–10	34 (11%)
>10	4 (1%)
Presentation	
Screening	73 (24%)
Bleeding	138 (46%)
Abdominal symptoms	69 (23%)
Other	22 (7%)
Urgency	
Elective	259 (86%)
Urgent	34 (11%)
Emergent	9 (3%)
Operation	
Left hemicolectomy	27 Open, 5 laparoscopic
Right hemicolectomy	127 Open, 24 laparoscopic
Sigmoid colectomy	54 Open, 4 Laparoscopic
Transverse colectomy	26 Open
LAR	17 Open, 3 laparoscopic
Total abdominal colectomy	8
Total proctocolectomy	4
Hartmann's procedure	3
Histology	
Ordinary	206 (68%)
Mucinous	30 (10%)
Features of MIS	20 (7%)
Dysplasia or well-differentiated CA in an adenoma	27 (9%)
Poorly differentiated	7 (2%)
Other (spindle cell, papillary, anaplastic, small cell)	12 (4%)
T Stage	
T1	43 (14%)
T2	47 (16%)
T3	177 (59%)
T4	28 (9%)
Benign	7 (2%)
N Stage	
NX	1 (<1%)
N0	175 (58%)
N1	71 (24%)
N2	48 (16%)
n/a	7 (2%)
M Stage	
M0	262 (87%)
M1	33 (11%)
n/a	7 (2%)
Overall Stage	
I	73 (24%)
IIA	92 (30%)
IIB	8 (3%)
IIIA	14 (5%)
IIIB	52 (17%)
IIIC	23 (8%)
IV	33 (11%)
n/a	7 (2%)
Adjuvant chemotherapy	
Yes	115 (38%)
None	169 (56%)
Unknown	18 (6%)

TABLE II. Relationship Between BMI, Age and Charlson Score and Morphometrics, and Between Morphometrics

	Average psoas density	Total psoas area	Visceral fat	Subcutaneous fat distance	Total body fat
BMI	−0.16 (−0.28, −0.04) $P = 0.009$	0.23 (0.11, 0.35) $P = 0.0002$	0.56 (0.47, 0.64) $P < 0.0001$	0.84 (0.80, 0.87) $P < 0.0001$	0.85 (0.82, 0.88) $P < 0.0001$
Age	−0.30 (−0.37, −0.22) $P < 0.0001$	−17.7 (−24.2,−11.2) $P < 0.0001$	1.38 (0.35, 2.42) $P < 0.0001$	−0.38 (−1.32, 0.56) $P =$ NS	0.99 (−1.05, 3.04) $P =$ NS
Charlson score	−1.72 (−2.18, −1.26), $P < 0.0001$	−32.5 (−72.1, 7.2) $P =$ NS	13 (7.1,18.9) $P < 0.0001$	1.20 (−4.46, 6.86) $P =$ NS	20.4 (8.3, 32.5) $P = 0.001$
Average psoas density	1	0.16 (0.04, 0.27) $P = 0.008$	−0.42 (−0.51, −0.32) $P < 0.0001$	−0.24 (−0.34, −0.12) $P < 0.0001$	−0.39 (−0.49, −0.29) $P < 0.0001$
Total psoas area		1	0.41 (0.31, 0.50) $P < 0.0001$	0.02 (−0.09, 0.14) $P =$ NS	0.40 (0.29, 0.49) $P < 0.0001$
Visceral fat			1	0.45 (0.35, 0.54) $P < 0.0001$	0.86 (0.82, 0.89) $P < 0.0001$
Subcutaneous fat distance				1	0.73 (0.67, 0.78) $P < 0.0001$
Total body fat					1

TABLE III. Relationship Between Morphometrics and Co-Morbidities

Variable	Cardiac disease mean (SD) yes vs. no	Pulmonary disease mean (SD) yes vs. no	Diabetes mean (SD) yes vs. no	Prior non-CRC cancer mean (SD) yes vs. no
Average psoas density	49.0 (8.4) vs. 55.9 (8.8), $P < 0.0001$	50.4 (8.7) vs. 54.3 (9.2), $P = 0.01$	51.2 (7.5) vs. 54.3 (9.5), $P = 0.01$	51.4 (7.8) vs. 54.2 (9.4), $P = 0.03$
Visceral fat area	208.9 (123.8) vs. 148.5 (100.9), $P = 0.0001$	204.4 (133.2) vs. 160.9 (107.0), $P = 0.06$	233.5 (112.5) vs. 152.7 (106.5), $P < 0.0001$	183.6 (114.5) vs. 163.5 (111.0), $P =$ NS
Subcutaneous fat area	178.5 (89.1) vs. 179.3 (103.2), $P =$ NS	200.8 (136.3) vs. 175.9 (92.2), $P =$ NS	231.8 (113.7) vs. 168.0 (92.4), $P = 0.001$	173.9 (95.9) vs. 180.1 (99.8),$P =$ NS
Total body area	836.8 (218.3) vs. 742.8 (209.9), $P = 0.001$	878.7 (281.3) vs. 755.2 (200.9), $P = -0.02$	927.8 (22.5) vs. 739.5 (201.6), $P < 0.0001$	785.2 (224.2) vs. 768.5 (215.3), $P =$ NS

Adjuvant chemotherapy was used in 113 patients (45.3%) and not in 158 patients (54.7%). For 18 patients, it was unclear whether they received adjuvant chemotherapy. The use of adjuvant chemo was significantly higher among patients with higher PD ($P = 0.003$) but did not correlate with any of the obesity measures, BMI or Charlson score.

Sarcopenia and Complications of Surgery

Overall 174 patients (58%) had some type of complication, which were categorized as either infectious or non-infectious. Infectious complications occurred in 90 patients, and primarily consisted of wound infections, which occurred in 44 patients (14.5%), but also included intraabdominal abscess (12), urinary tract infections (24), septicemia (3), pneumonia (10), and C. Diff colitis (8). Some patients had more than one complication. Non-infectious complications primarily consisted of prolonged ileus requiring a longer hospital stay (26) and bleeding complications (14), but also included DVT or PE (5), post-operative rhythm disturbances (4) and other complications. Twenty-six patients had both an infectious and non-infectious complication.

The single best predictor of any complication versus none was PD (OR 0.96 (0.94, 0.99), $P = 0.004$). When considering PD, Charlson score, age or any specific co-morbidity (cardiac disease, pulmonary disease, or diabetes) were not statistically significant. We further broke down non-infectious versus infectious complications. On univariate analysis, the probability of developing an infectious complication was significantly associated with both decreasing PD ($P = 0.03$) and increasing SFD ($P = 0.003$). Neither the Charlson Comorbidity Index, age or BMI was significantly associated with an infectious complication ($P = 0.10$ and $P = 0.63$, respectively). There was also no significant association between infectious complications and cardiac disease ($P = 0.74$), pulmonary disease ($P = 0.10$) and diabetes ($P = 0.64$). On multivariate analysis, the strongest predictor of an infectious complication was PD [OR 0.95 (0.93, 0.98) for every unit change, $P = 0.001$].

When this was further broken down to look specifically at wound infections, univariate analysis found that a wound infection was significantly more likely in patients with increased obesity, regardless of how you measured it. There was no correlation between development of a wound infection, age or specific co-morbidities (cardiac disease, pulmonary disease, diabetes or prior cancer). Using backwards selection, the single best predictor of a wound infection following colon cancer surgery was SFD (OR 1.05 (1.02, 1.08) for every unit change of 10, $P = 0.003$).

Sarcopenia and Colon Cancer Outcomes

To study whether morphomics may be related to tumor biology in colon cancer, we examined both stage at presentation and outcomes. Patients who had colectomy for what turned out to be benign disease were excluded. None of the measurements of sarcopenia (PD) or obesity (VF, SFD, TBF, or BMI) correlated with histology, T-stage or N-stage. Even comparing patients with liver metastases (M1) to those without (M0), there was no significant difference in any measure. The lack of correlation between M stage and PD suggests that the presence of sarcopenia in these patients does not appear to be related to tumor burden. Overall American Joint Commission on Cancer (AJCC) Stage also did not correlate with any of the morphometric measurements.

The median follow-up for this patient population was 2.81 years (mean of 3.23 years). At the time of the last follow-up, 65% were alive without disease and 12 patients (4%) were alive with disease. There were 92 patients who died, 48 (16%) having succumbed to metastatic colorectal cancer while 44 (15%) died without evidence of disease. Excluding the patients with M1 disease, or those patients undergoing colectomy for what turned out to be benign disease, we examined the impact of morphometrics on disease-free and overall survival in the context of Charlson score. On initial univariate analysis, PD, TBF, and Charlson score were significantly associated with both disease-free and overall survival, as shown in Table IV. Final multivariate models for DFS and OS were controlled for both age and Charlson score. After controlling for these, PD was no longer a significant predictor of outcome. However, TBF was still significantly associated with outcome. Our final multivariate Cox model for DFS included age, Charlson co-morbidity index, nodal positivity, and TBF (Table V).

DISCUSSION

Cancer of the colon and rectum is the 4th most common malignancy in the United States, with an estimated incidence of 141,210 new cases in 2011 [25]. The majority of these patients are candidate for curative resection, an operation that unfortunately carries a high risk of complication, with morbidity ranging from 20% to 45% [26–29]. Numerous risk factors have been associated with the occurrence of postoperative complications in colorectal surgery, including age, BMI, the presence of excess SFD, presence of diabetes, and nutritional status as reflected by serum albumin level. Operative process measures associated with postoperative complications include duration of operative procedure, the receipt of blood transfusion, glycemic control, intraoperative hypothermia, and the timing and dosing of perioperative antibiotics.

Patient frailty has been considered to be a risk factor for adverse postoperative outcomes, but is poorly quantified. Frailty has been defined as a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems and causing vulnerability to adverse outcomes [30]. However, assessment of frailty is difficult, typically depending on multiple subjective evaluations. Muscle density (also known as muscle attenuation or myosteatosis), may serve as one objective measure of frailty, as it is not only related to age, but also inactivity, weight gain, insulin resistance, and metabolic status [31,32]. It has been associated with abnormalities in glucose metabolism, type 2 diabetes and levels of several inflammatory mediators including leptin, C-reactive protein (CRP), IL-6, and tumor necrosis factor-alpha (TNF-α) [33–39]. Trunk muscle attenuation, as measured in this study, is strongly associated with functional capacity, impaired physical function and increased risk of disability and injury in older adults [40–42]. Muscle attenuation also

TABLE IV. Significant Associations Between Morphomics and Outcome on Univariate Analysis

	Disease-free survival		Overall survival	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Total body fat (change of 10)	1.01 (1.00, 1.03)	0.03	1.01 (1.00,1.03)	0.04
Average psoas density (change of 1)	0.97 (0.95, 1.00)	0.03	0.97 (0.95, 1.00)	0.04
Charlson co-morbidity index (change of 1)	1.27 (1.10, 1.48)	0.002	1.43 (1.21, 1.68)	<0.0001

TABLE V. Best Multivariate Cox Model for Disease-Free Survival

Variable	Comparison	HR (95% CI)	*P*-value
Age	+1 year	1.03 (1.00, 1.06)	0.08
Charlson score	+1 point	1.11 (0.89, 1.39)	0.36
Lymph node positive	Yes vs. no	1.75 (1.07, 2.87)	0.03
Total body fat	+10	1.01 (1.00, 1.02)	0.03

occurs in the muscles of young individuals with limited physical activity, weight gain and metabolic abnormalities [43], and as such may identify high-risk patients irrelevant of chronologic age.

Indeed, PD was the single best predictor of whether the patient had any complication, including both non-infectious and infectious complications. When breaking down the infectious complications even further, PD was highly predictive of non-wound infections while SFD was the best predictor of a wound infection, consistent with previous observations [11]. Neither the Charlson Comorbidity Index, age nor BMI were accurate predictors of these complications when morphometrics were taken into account. It is telling that while decreased PD was associated with multiple co-morbid conditions, it was the significant predictor while the presence of these conditions was not. This suggests that it is the impact of these conditions on the patient that increases risk rather than the condition itself. Typically surgeons base their estimate of risk on the past medical history, but more objective measurements of the biologic impact of these co-morbidities may be a better method to identify patients whereby risk outweighs benefit.

This information, readily available from the preoperative CT scan may allow for preoperative intervention and a reduction in surgical complications. Frail patients (of all ages) are less able to participate in the standard post-operative recovery program, including early ambulation and incentive spirometry, which may lead to increased surgical complications (venous thromboembolism, prolonged ileus, pneumonia) [8,44–46].

Exercise training, in general, can rapidly and significantly improve both aerobic capacity and strength of individuals, especially de-conditioned older individuals [47–49]. Preoperative interventions in frail patients with osteoarthritis and colon cancer have shown rapid increases in patients' strength and walking capacity, in less than 4 to 6 weeks [50,51]. Mayo et al. [50,52] showed that for patients undergoing scheduled colorectal surgery, including cancer, a prehabilitation program consisting of walking and breathing exercises, could improve functional exercise capacity and this was associated with improved postoperative recovery. Based on these findings, the University of Michigan has developed a targeted exercise intervention to increase the muscular strength of older surgery patients needing colon surgery. This program involves pedometer based walking programs which have demonstrated excellent compliance, improvements in exercise outcomes, and improved patient satisfaction [53–56].

The specific impact of prehabilitation programs on muscle attenuation is less clear. Several studies have shown that a directed exercise program can improve muscle attenuation. Taaffe et al. [57] demonstrated how resistance exercises can impact muscle attenuation, with decreases in fatty infiltration with exercise and increases after cessation. Coker et al. [58] showed that a 12-week high intensity aerobic exercise program significantly improved muscle attenuation. Hutchinson et al [59] showed how a 12-week treadmill-based program could improve muscle attenuation among women with polycystic ovary syndrome, which is characterized by an insulin resistant state. However, these studies focused on thigh muscle attenuation, not trunk muscles such as the psoas. What type of exercises might be best to improve PD is less clear. It also remains unknown whether exercise-based improvements in muscle density would be associated with concurrent improvements in glucose metabolism, insulin resistance, levels of pro-inflammatory cytokines, and whether this might improve surgical outcomes. Further research is warranted, and is on-going at the University of Michigan.

We have previously reported the impact of sarcopenia on long-term outcomes among patients with stage III melanoma and found that decreased psoas muscle density on CT was a highly significant predictor of outcome, along with tumor factors such as Breslow thickness and ulceration, suggesting the biology of the host may impact the natural history of the disease [10]. These results are not completely surprising given the long-theorized relationship between melanoma and the immune system. A similar relationship is less well-developed for colorectal cancer. In this study, fatty infiltration of the psoas muscle was not associated with stage of disease. While it was associated with both DFS and OS on univariate analysis, after controlling for both age and Charlson score, this was no longer significant. A more careful analysis shows that PD was primarily predictive of non-colorectal cancer deaths among these patients, suggesting that frailty (and perhaps the metabolic or immunologic correlates) play less of a role in the natural history of colorectal cancer than melanoma. This data is in line with data recently reported by Peng et al. [60], who found that sarcopenia was not associated with long-term outcome among patients with colorectal cancer metastases to the liver undergoing hepatic resection.

Total body fat, however, was a significant predictor of outcome, and figured into our best-fit multivariate Cox model for DFS along with age, the Charlson co-morbidity index and nodal involvement. While the relationship between obesity and colorectal outcomes has been well described, in most cases obesity is defined by BMI. However, there is wide variation in how precisely BMI describes body composition [61–63]. Our results are consistent with others that have demonstrated that more direct measurements of adiposity may predict colorectal cancer outcomes better than BMI [64,65]. The impact of obesity on colorectal cancer biology may be connected to adiposity, with proposed mechanisms including alterations of glucose-insulin dynamics, hyperinsulinemia and insulin-like growth factors, or estrogen production by adipose tissue [66–70]. As BMI can be impacted by muscle mass, direct measures of adiposity, such as morphometric measurements, may better elucidate risk.

In conclusion, analytic morphometric analysis provided objective data that stratified both complications of treatment and outcome better than commonly used variables (age, BMI, co-morbidities) among patients with colorectal cancer. Specifically, decreasing PD is a significant predictor of surgical complications, increasing SFD is a significant predictor of wound infection and TBF is a significant predictor of outcome. Morphometric analysis of patients being considered for colectomy is readily available data that may help identify patients at increased risk of surgical complication, and may help with adjuvant therapy decisions. Further research into the impact that pre-surgical conditioning may have on reversing sarcopenia and adiposity, and thus decreasing surgical complications and improving outcomes, are on-going.

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