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S184: preoperative sarcopenia is associated with worse short-term outcomes following transanal total mesorectal excision (TaTME) for rectal cancer

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Abstract

Introduction Malnutrition and deconditioning impact postoperative morbidity and mortality. Computed tomography (CT) body composition variables are used as markers of nutritional status and sarcopenia. The objective of this study is to evaluate the impact of sarcopenia, using CT variables, on postoperative outcomes following transanal total mesorectal excision (TaTME) for rectal cancer.

Methods This was an institutional retrospective cohort analysis of consecutive rectal cancer patients who underwent TaTME between April 2014 and May 2020. Psoas muscle index (PMI) was calculated from diagnostic CT scans. Based on previous studies, patients in the lowest PMI tertile by gender were considered sarcopenic. Fisher's exact and Mann–Whitney U test were used to compare categorical and continuous variables, respectively. Readmission rates and postoperative complications were compared between groups. Backward stepwise logistic regression was used to determine the association between sarcopenia and 30-day postoperative complications.

Results 85 patients were analyzed, of which 63% were male, with a median age of 59 (IQR: 51–65), and median BMI of 28 (IQR: 24–32). Of the entire cohort, 34% ($n=29$) were sarcopenic (median PMI 5.39 IQR: 4.49–6.71). No significant difference in baseline characteristics between sarcopenic and nonsarcopenic patients were observed. 55% of sarcopenic patients experienced a complication within 30 days compared to 24% of nonsarcopenic patients ($p=0.01$). 41% of sarcopenic patients required hospital readmission within 30 days compared to 17% of their nonsarcopenic counterparts ($p=0.014$). Sarcopenic patients also experienced significantly higher rates of post-operative small bowel obstruction (10% vs. 0%, $p=0.04$). Multi-variable analyses identified that sarcopenic patients have a fourfold increase in odds of experiencing a 30-day postoperative complication (OR: 4.44, 95%CI: 1.6–12.4, $p<0.05$) after adjusting for gender.

Conclusion Preoperative sarcopenia is associated with increased 30-day postoperative complications following TaTME for rectal cancer. Postoperative complications can have serious oncologic implications by delaying adjuvant chemotherapy. Therefore, preoperative recognition of sarcopenia prior to undergoing TaTME for rectal cancer may provide an opportunity for early intervention with prehabilitation programs.

Keywords TaTME · Sarcopenia · Laparoscopy · Malnutrition · Rectal cancer

Despite significant advances in multidisciplinary approaches to rectal cancer management, surgery remains the foundation

of treatment. Total mesorectal excision (TME) is the current standard of care when performing a proctectomy due to its significant impact on the reduction of local recurrence and improved postoperative function [1–3]. Transanal TME (TaTME) is an emerging minimally invasive surgical technique with several technical advantages that utilizes a “bottom-up” approach when performing the TME [4].

Postoperative morbidity following proctectomy, specifically TaTME for rectal cancer, remains moderately high [5–12]. With an aging population that is at greater risk for

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developing postoperative complications, early preoperative identification using established prognostic factors for surgical morbidity allows for modification and optimization of treatment plans. Historically, this patient cohort has been identified by a subjective “end-of-the-bed” frailty assessment during initial surgical presentation. There is significant heterogeneity in the methods used by clinicians to assess preoperative frailty and physiological reserve. There is no standard, single operational definition of frailty. Furthermore, no single comprehensive screening or assessment tool has been developed, making consistent identification of these patients difficult [13].

Various forms of body composition analyses have been identified as predictors of postoperative complication following surgery for gastrointestinal malignancy [14–16]. Preoperative sarcopenia and increased adiposity have been negatively associated with short- and long-term outcomes in gastrointestinal malignancy [17–24]. Sarcopenic patients have major alterations in nutritional and immunologic parameters culminating in a progressive state of catabolism and reduced anabolism, which influence their ability to manage the physiological stress of disease and surgery [25].

Given our current understanding of the relationship between sarcopenia and postoperative outcomes, it is important to further characterize these prognostic factors when new techniques such as TaTME emerge. To date, no study has identified the effects of frailty or body composition predictors on postoperative outcomes in patients undergoing TaTME for rectal cancer. Therefore, the primary purpose of this study was to determine the potential impact of sarcopenia on short-term postoperative outcomes in patients undergoing TaTME for stage I–IV rectal cancer.

Methods

Study population

All patients who underwent TaTME for rectal cancer at a single institution between April 2014 and May 2020 were included in this retrospective cohort analysis. Computed tomography (CT) scans were reviewed from the time of diagnosis and following neoadjuvant therapy. Baseline demographic information, disease and perioperative patient characteristics were collected along with 30-day complication and readmission rates.

Body composition evaluation and analysis

CT scans obtained at the time of rectal cancer diagnosis were used for our body composition analysis. Axial images were selected at the level of the middle of the third lumbar vertebral body. All body composition data were extracted

by researchers (JS, DC, and DC) who underwent training by expert radiologists using Aquarius iNtuition Edition Ver.4.4.13.P4 software (TeraRecon, Durham, North Carolina, USA). Sarcopenia was assessed by manually measuring the cross-sectional area of the right and left psoas muscle outline individually with a polygon tool. This technique is consistent with previously published similar methodology. [21, 26–28] Once the muscle was outlined accurately, an automatic calculation of the area of pixels with attenuation between – 29 and 150 Hounsfield units (HU) was performed (Fig. 1). This HU range excluded vasculature and fatty infiltration. The total psoas area was standardized as the psoas muscle index (PMI) by calculating the sum of the right and left psoas area values and dividing this total psoas area by the square of the patient’s height in meters (cm^2/m^2). This study was approved by the University of Massachusetts Medical School Institutional Review Board (study# H00013567).

Statistical analysis

Results are presented as frequencies and percentages for categorical variables, and medians and interquartile ranges for continuous variables. The definition of sarcopenia has thus far been study-specific. Researchers have used different methods to differentiate between sarcopenic and non-sarcopenic patients, none of which have been proven to be superior [27–31]. A common method, which we adopted for the present study, is to use sex-specific PMI tertiles with

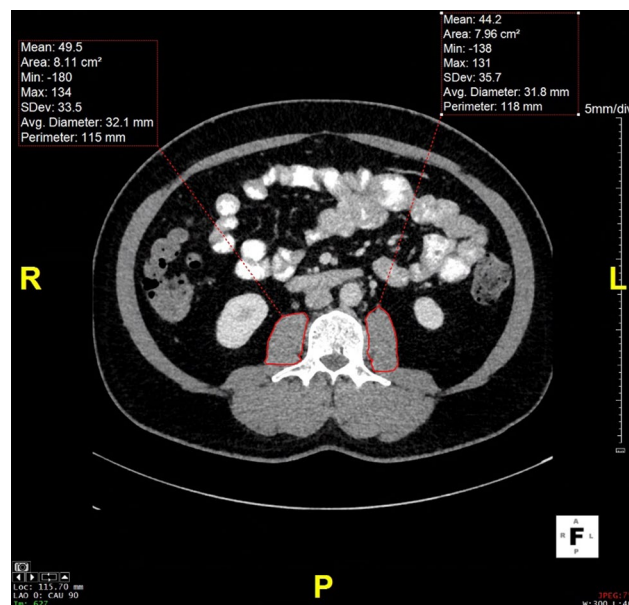


Fig. 1 Representative psoas muscle index [psoas muscle area/height (m^2)] measurement using cross-sectional computed tomography at the third lumbar level (L3)

patients falling in the lowest tertile being considered sarcopenic. Patients were divided into tertiles based on gender. Sarcopenic patients had PMI measurements in the lowest tertile (4.11 or lower for females, 5.37 or lower for males). Fisher's exact test and the Mann–Whitney U test were used to compare categorical and continuous variables, respectively. Stepwise backwards selection was used to fit a logistic regression model to determine the association of sarcopenia and any 30-day postoperative complication. A p value of 0.05 was considered statistically significant. All analyses were performed using SAS version 9.4.

Results

A total of 127 patients underwent a TaTME between April 2014 and May 2020 at a single high-volume colorectal surgery practice. 24 patients were excluded because they underwent proctectomy with TaTME for an indication other than rectal cancer (i.e., inflammatory bowel disease, non-malignant polyp). An additional 18 patients were excluded because their diagnostic CT scan was performed at another institution and not available for body composition analytics.

Table 1 presents the baseline patient characteristics for all patients who were included in the final analysis. Overall, 85 patients were identified and 34% of those patients were classified as sarcopenic based on their PMI being lowest tertile. Our sample was predominantly male (63%), with a median age 59 (IQR 51–66), BMI 28 (IQR 24–32), and PMI 5.39 cm²/m² (what's the IQR >). There were no significant differences in the demographic characteristics, baseline comorbidities (i.e., HTN, DM2), and clinical or

pathologic TNM stage between sarcopenic and non-sarcopenic patients ($p > 0.05$).

Table 2 presents the perioperative and disease-specific characteristics for all patients included in the final analysis. Median operating time was 309 min (IQR 257–370) and blood loss was 100 cc (IQR 50–100) with no differences observed between sarcopenic and non-sarcopenic groups (309 min vs. 310 min, $p = 0.35$ and 100 cc vs. 95 cc, $p = 0.56$, respectively). The majority of patients had a stoma created at the time of surgery and 94% of the sample had received neoadjuvant chemotherapy and radiation. There were no statistically significant differences noted in the number of stomas created, receipt of neoadjuvant chemotherapy and radiation, and distance of the rectal tumor from the anal verge on rigid proctoscopy between sarcopenic and non-sarcopenic groups.

Tables 3 and 4 presents the 30-day postoperative outcomes including readmission rates, medical and surgical complications. Sarcopenic patients had a significantly higher overall 30-day postoperative complication rate compared to non-sarcopenic patients (55% vs. 24%, $p = 0.005$). Multivariable logistic regression revealed that sarcopenic patients have a fourfold increase in odds of 30-day postoperative complication (OR 4.44, 95%CI 1.6–12.4, $p < 0.05$) after adjusting for gender. Readmission to hospital occurred in 25% of patients within 30 days of surgery and there were significantly more readmissions in sarcopenic patients compared to non-sarcopenic (41% vs. 17%, $p = 0.01$). There were also significantly more small bowel obstructions in sarcopenic patients compared to their non-sarcopenic counterparts (10% vs. 0%, $p = 0.04$). There were no patient deaths within 30 days of surgery.

Table 1 Baseline characteristics of patients who underwent trans-anal total mesorectal excision for rectal cancer

Patient characteristics	Total $n = 85$	Non-sarcopenic $n = 56$	Sarcopenic $n = 29$	p value
Median age (IQR)	59 (51–66)	59 (51–66)	59 (55–66)	0.52
Median BMI (IQR)	28 (24–32)	29 (24–33)	27 (24–30)	0.10
Male	52 (63)	34 (63)	18 (62)	0.94
Comorbidities				
HTN	32 (39)	24 (45)	8 (28)	0.12
DM	15 (19)	10 (19)	5 (18)	0.88
Smoker	18 (22)	8 (15)	10 (34)	0.11
CHF	1 (1)	1 (2)	0	0.99
Steroid use	3 (4)	1 (2)	2 (7)	0.28
ASA score				
1	1 (1)	1 (2)	0	0.22
2	53 (65)	31 (58)	22 (76)	
3	28 (34)	21 (40)	7 (24)	

Values represent n (%) unless otherwise specified

IQR interquartile range, BMI body mass index, HTN hypertension, DM diabetes mellitus, CHF congestive heart failure, ASA American Society of Anesthesiologists physical status classification

Table 2 Baseline perioperative and disease-specific characteristics of patients who underwent trans-anal total mesorectal excision for rectal cancer

	Total <i>n</i> = 85	Non-sarcopenic <i>n</i> = 56	Sarcopenic <i>n</i> = 29	<i>p</i> value
Perioperative characteristics				
Median OR time (IQR)	309 (257–370)	310 (265–395)	309 (233–344)	0.35
Median EBL (cc) (IQR)	100 (50–100)	95 (50–100)	100 (50–100)	0.56
Stoma				0.81
No stoma	1 (1.3)	1 (1.9)	0	
Ileostomy	71 (89)	45 (87)	26 (93)	
Colostomy	8 (10)	6 (12)	2 (7)	
Anastomosis				0.93
Handsewn	10 (12)	6 (11)	4 (14)	
Stapled	60 (73)	39 (74)	21 (73)	
No anastomosis	12 (15)	8 (15)	4 (14)	
Disease characteristics				
Neoadjuvant therapy	69 (85)	45 (87)	24 (83)	0.74
CTX + RT	65 (94)	42 (93)	23 (96)	0.42
RT alone	1 (2)	0	1 (4)	
CTX alone	1 (2)	1 (2)	0	
CTX followed by CTX + RT	2	2	0	
Median distance from AV on RP (cm)	7.0 (5–8)	7.0 (5–8)	6.5 (3–8)	0.74
Median distance from AV on MRI (cm)	8.0 (5–9)	8.0 (5–10)	7.0 (6–9)	0.80

Values represent *n* (%) unless otherwise specified

OR operating room, EBL intraoperative estimated blood loss, CTX chemotherapy, RT radiotherapy, AV anal verge, RP rigid proctoscopy, MRI magnetic resonance imaging

Table 3 The association between sarcopenia and any 30-day postoperative complication

Postoperative outcome	Total <i>n</i> = 85	Non-sarcopenic <i>n</i> = 56	Sarcopenic <i>n</i> = 29	<i>p</i> value
Any 30-day outcome	29 (34)	13 (24)	16 (55)	0.005
Ileus	12 (14)	5 (9)	7 (24)	0.10
Urinary retention	4 (5)	2 (4)	2 (7)	0.61
Readmission	21 (25)	9 (17)	12 (41)	0.014
SSI	4 (5)	2 (4)	2 (7)	0.61
SBO	3 (4)	0	3 (10)	0.04
UTI	1 (1)	1 (2)	0	0.99
Anastomotic leak	2 (2)	2 (4)	0	0.54
Pelvic abscess	7 (8)	4 (7)	3 (10)	0.69
Renal failure	1 (1)	1 (2)	0	0.99
Pneumonia	0	0	0	n/a
Cardiovascular event	1 (1)	0	1 (4)	0.35
DVT	0	0	0	n/a
PE	0	0	0	n/a
Sepsis	2 (2)	1 (2)	1 (4)	0.99
Reoperation	2 (2)	1 (2)	1 (4)	0.99
Unplanned SICU admission	7 (8)	4 (7)	3 (10)	0.69
Other	9 (11)	5 (9)	7 (14)	0.71

Values represent *n* (%) unless otherwise specified

SSI surgical site infection, SBO small bowel obstruction, UTI urinary tract infection, DVT deep venous thrombosis, PE pulmonary embolism, SICU surgical intensive care unit

Table 4 Logistic regression predicting 30-day complication ($n=83^*$)

	Odds ratio	95% CI	<i>p</i> value
Sarcopenic	4.44	1.60–12.38	0.004
Male gender	3.87	1.26–11.89	0.018

*Two patients were not included in the logistic regression because of missing data

$c=0.72$

Discussion

TaTME is emerging as a minimally invasive surgical technique for the treatment of rectal cancer. High quality evidence on the impact of preoperative frailty on postoperative outcomes in patients undergoing TaTME is lacking. The present study identified that nearly 35% of patients undergoing TaTME for rectal cancer, fall within the lowest PMI tertile and are considered sarcopenic [29–31]. After adjusting for gender, sarcopenic patients had a nearly fourfold higher odds of experiencing a postoperative complication within 30 days compared to nonsarcopenic patients. Specifically, a pairwise analysis showed that sarcopenic patients were more likely to experience a small bowel obstruction or hospital readmission within 30 days of undergoing a TaTME.

Identification of preoperative prognostic factors with the aim of reducing postoperative morbidity is critical in cancer patients due to the need of timely initiation of adjuvant treatments such as chemotherapy. Frailty has consistently been shown to negatively impact postoperative outcomes [32] though it has historically been difficult to objectively measure. Quantitative metrics such as sarcopenia have been shown to be a more pragmatic tool when assessing frailty and physiological reserve [22, 33–35].

Several studies have demonstrated the negative association between sarcopenia and postoperative outcomes in colorectal cancer patients [14, 20, 21, 36, 37], inflammatory bowel disease [38], pancreatic malignancy [27], and following hepatobiliary resection [28]. In a recent retrospective analysis of 350 patients undergoing colorectal cancer resection, Richards et al. demonstrated that 32.9% of the cohort was classified as sarcopenic which was consistent with our cohort's sarcopenia rate of 34% [36]. The prevalence of sarcopenia ranges between 39 and 48% in colorectal malignancy, regardless of tumor stage, differentiation, age, or gender [20]. This baseline compromised and frail state prior to any treatment raises concern, particularly as surgical and medical treatments carry intrinsic risks of deconditioning. Similar to our findings, Richards et al. identified sarcopenia as being a significant predictor of any complication. The authors also found that sarcopenia adversely impacts mortality, length of stay, and discharge to a care facility [36]. Lastly, Jones et al. who measured sarcopenia

using cross-sectional muscle mass measurements, found significantly increased rates of major complications (Clavien–Dindo > III). However, as seen in this study, there were no differences in hospital length of stay or mortality [39].

The present study identified that sarcopenic patients experience higher rates of small bowel obstruction in the immediate post-operative period. It is currently unclear as to the exact pathophysiologic relationship between sarcopenia and bowel obstructions. Lieffers et al. also found higher rates of bowel obstruction in sarcopenic patients undergoing resection for stage II–IV colorectal cancer compared to non-sarcopenic patients [40]. Additionally, weight loss and hypoalbuminemia, both of which are associated with sarcopenia, have also been associated with early postoperative small bowel obstruction [41]. In the present study, sarcopenic patients had more than twice the rate of 30-day hospital readmissions of their non-sarcopenic counterparts. This is of concern particularly as hospital readmissions contribute to patient dissatisfaction, and carry considerable added cost and healthcare resource utilization [42]. As the present study was not designed to identify the specific reason for readmission, we hypothesize that generalized frailty and poor physiologic reserve were major contributors to readmission in our sample.

The majority of patients undergoing treatment for rectal cancer will require some form of neoadjuvant chemotherapy or radiation prior to surgical resection [43]. Therefore, when studying the effects of sarcopenia in colorectal malignancy, it is important to differentiate colon from rectal cancer, as neoadjuvant therapy confers considerable morbidity and mortality independent of surgery [44]. In addition to the toxic effects of chemoradiation, sarcopenia has also been independently associated with poor response to chemoradiation in locally advanced rectal cancer [45]. Few studies have specifically assessed the postoperative outcomes in sarcopenic patients with rectal cancer. In a retrospective review of 188 patients undergoing rectal cancer resection, Choi et al. identified that sarcopenia is an independent predictor of reduced overall survival [21]. In another study by Chung et al., sarcopenia and a reduction in muscle mass by approximately 4% significantly affected overall survival in patients with locally advanced disease [46]. However, no TaTMEs were performed in these studies and all patients underwent either laparoscopic or open resection with TME.

This study is the first to assess the effects of sarcopenia in a select population undergoing an emerging surgical technique. Additionally, we were able to capture detailed perioperative and disease characteristics such as TNM staging, tumor location, details regarding chemotherapy and radiation treatment, and surgical technique including ostomy and anastomosis details. As there is significant heterogeneity in the literature on how to technically measure muscle mass and define sarcopenia, the interpretation

of results across studies should be approached with caution. We undertook a similar method to previous studies which included measuring a standardized form of psoas muscle area and defining sarcopenia as those patients falling into the lowest tertile [47]. Additionally, we are confident that our cohort has a similar body composition profile when compared to healthy patients as our lowest tertile PMI cutoffs in females (4.11) and in males (5.37) were comparable to previous studies [26].

There are however several limitations to this study. First, the small sample size and number of outcomes limited our assessment of long-term mortality and oncologic outcomes, including local and distant recurrence, and disease-free survival. Larger studies would be required to perform a more thorough analysis on these variables. Second, this is a single institution, retrospective study which is susceptible to selection bias and limits overall generalizability. Thirdly, there is an opportunity for additional selection bias due to the 18 patients that were not included in the final analysis due to missing or inaccessible CT scans. However, given that these patients were both from within our institution and from other outside institutions, the potential bias is likely negligible. Finally, our determination of sarcopenia was based solely on PMI analysis; however, several other markers such as prealbumin levels are used by clinicians as a proxy for malnutrition. Due to the retrospective nature of the present study, we were unable to incorporate biochemical markers such as albumin, prealbumin, and liver function tests into our analysis.

Sarcopenia has been associated with impairment of physical performance, increased postoperative morbidity, and cancer-specific survival. Given that all rectal cancer patients will have some form of cross-sectional imaging for oncologic staging, measuring muscle mass variables using standardized tools is easy, convenient, and reproducible. Clinicians can incorporate this knowledge when formulating treatment plans for high-risk sarcopenic patients including the type of neoadjuvant therapy, adjustments in dosing or duration, and/or the incorporation of multimodal prehabilitation programs. Although there is currently conflicting evidence on whether prehabilitation programs in colorectal surgery consistently improve outcomes, this debate may be due to the heterogeneity of existing programs and lack of patient customization [48, 49]. As, several studies have shown some benefit to transdisciplinary prehabilitation programs (i.e., physical therapy, diet optimization) in the reversal of sarcopenia, increased utilization of such programs should be considered prior to the initiation of rectal cancer treatment [50–52].

Conclusion

A large proportion of rectal cancer patients are considered frail and sarcopenic, both of which are poor prognostic factors following treatment. This study has demonstrated that sarcopenic patients undergoing TaTME for rectal cancer can be easily and objectively identified using their diagnostic CT scan, and that preoperative sarcopenia is associated with increased 30-day postoperative complications. Early identification of this high-risk group which typically undergoes multimodal systemic therapy including surgery can allow clinicians to proactively intervene using strategies such as transdisciplinary prehabilitation to optimize patient outcomes.

Author contributions Dr. JES, Dr. KA, and Dr. CB were responsible for the conception, design, data analysis, and editing of this manuscript. Dr. JES, Dr. DC and Ms. DC were responsible for data collection and Ms. AC was responsible for data analysis. Dr. JAB, Dr. LJM, Dr. JSD, Dr. PRS, and Dr. JAM contributed to the design, interpretation of the data, and revisions for the final approval of this manuscript. All authors provided substantial contributions to this manuscript.

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Declarations

Disclosures Justin A. Maykel MD—Applied Medical Clinical Educator. Jeremy E. Springer MD, Catherine Beauharnais MD, Derek Chicarilli MD, Danielle Coderre BS, Allison Crawford MS, Jennifer A. Baima MD, Lacey J. McIntosh DO, Jennifer S. Davids MD, Paul R. Sturrock MD, and Karim Alavi MD have no conflict of interest or financial ties to disclose.

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