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Total energy expenditure in patients with colorectal cancer: associations with body composition, physical activity, and energy recommendations

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Short running head: Energy expenditure in colorectal cancer

Abbreviations used: ^2H , deuterium; ^{18}O , oxygen 18; ASMI: appendicular skeletal muscle index; BMI, body mass index; c_{H} deuterium pool size; c_{O} , oxygen 18 pool size; CO_2 , carbon dioxide; CRC: colorectal cancer; DLW: doubly labeled water; DRI, dietary reference intake; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; IPAQ, international physical activity questionnaire; IQR, interquartile range; k_{H} , deuterium loss from total body water; k_{O} , oxygen 18 loss from total body water; MET, metabolic equivalency of tasks; N_{H} , deuterium dilution space; N_{O} , oxygen 18 dilution space; O_2 , oxygen; PAL, physical activity level; PG-SGA, patient generated subjective global assessment; RAEE, residual activity energy expenditure; REE, resting energy expenditure; TEE, total energy expenditure

ClinicalTrials.gov identifier: NCT03131921; <https://clinicaltrials.gov/ct2/show/NCT03131921>

1 **Abstract**

2 **Background:** Total energy expenditure (TEE) data in patients with earlier stage cancer
3 is scarce, precluding an understanding of energy requirements.

4 **Objective:** The objective was to cross-sectionally characterize TEE in patients with
5 colorectal cancer (CRC) and to compare measured TEE to energy recommendations. It was
6 hypothesized that TEE would differ according to body mass, body composition, and physical
7 activity level (PAL) and current energy recommendations would have poor individual-level
8 accuracy.

9 **Design:** Patients with newly-diagnosed CRC had resting energy expenditure (REE) measured by
10 indirect calorimetry and TEE by doubly labeled water. Hypermetabolism was defined as REE >
11 110% predicted from the Mifflin St.-Jeor equation. Body composition was assessed via dual X-
12 ray absorptiometry. Physical activity was determined as the ratio TEE:REE (PAL) and residual
13 activity energy expenditure (RAEE). TEE was compared to energy recommendations of 25-30
14 kcal/day and dietary reference intakes (DRI) using Bland-Altman analyses. Patients were
15 stratified according to median body mass index (BMI), PAL, and sex-specific fat mass (FM) to
16 fat-free mass (FFM) ratio (FM:FFM).

17 **Results:** Twenty-one patients (M:F 14:7; BMI: 28.3±4.9kg/m², age: 57±12years) were included.
18 Most (n=20) had stage II-III disease; 1 had stage IV. Approximately half (n=11) were
19 hypermetabolic; TEE was not different in those with hypermetabolism and REE as a percent of
20 predicted was not correlated to TEE. TEE was 2473±499 kcal/day (range: 1562, 3622), or
21 29.7±6.3 kcal/kg body weight (range: 20.4, 48.5). Mean PAL was 1.43±0.27. Energy
22 recommendation of 25 kcal/kg underestimated TEE (-12.6±16.5%, P = 0.002); all energy
23 recommendations had wide limits of agreement (smallest was DRI: -21.2, 29.3%). Patients with

24 higher BMI and FM:FFM had higher bias using kcal/kg recommendations; bias from several
25 recommendations was frequently lower in patients with higher PAL and RAEE.

26 **Conclusions:** TEE variability was not reflected in energy recommendations and error
27 was influenced by body weight, body composition, and physical activity.

28 **Key words:** Energy expenditure, energy metabolism, cancer, energy requirements, energy
29 balance, nutritional assessment, dietary intake, body composition, physical activity

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46 **Introduction:**

47 Energy balance is the long-term relationship between energy intake and total energy
48 expenditure (TEE; sum of energy required for bodily maintenance at rest, movement, and food
49 digestion, absorption, and transport). Characterizing TEE is therefore essential for understanding
50 energy requirements needed to support or modulate energy balance. This concept is especially
51 relevant for individuals with cancer since body weight and body composition changes (i.e. loss
52 of fat-free mass, FFM) can be detrimental to prognosis (1–3). Conversely, weight gain during
53 cancer treatment may not confer a survival advantage in some circumstances (1), might worsen
54 pre-existing comorbidities, and increase secondary disease risk in patients with obesity (4,5).

55 In oncology, most of our understanding of energy expenditure comes from studies of
56 resting energy expenditure (REE), which is the largest component of TEE in non-athletic
57 populations. However, in patients with cancer, REE might be affected by changes in body
58 composition, systemic inflammation or tumor burden and may not correlate to TEE (6). Since the
59 ratio of TEE to REE is indicative of physical activity level (PAL), absence of a relationship
60 between REE and TEE indicates that variable physical activity might impact TEE within this
61 population, rather than REE alone.

62 To date, only four reports have measured TEE in cancer using objective and accurate
63 techniques such as doubly labeled water (DLW) or bicarbonate-urea (6–9), which severely limits
64 current understanding of energy requirements in oncology settings. The majority of patients in
65 these previous studies had advanced (i.e. stage IV) disease (6) or severe weight loss (i.e. 19% of
66 pre-illness body weight)(7). However, this likely represents a small proportion of patients with
67 certain types of cancer. For example, colorectal cancer (CRC) is the third most commonly
68 diagnosed cancer in the World (10); improvements in screening practices, lower incidence of risk
69 factors, and effective treatments options has led to a higher proportion of cancer cases diagnosed

70 at earlier stages (11), where severe wasting/weight loss (i.e. cachexia (12)) and high systemic
71 inflammation is less common (13). These patients also have a high prevalence of obesity at
72 diagnosis and weight gain during curative-intent treatment (14).

73 Due the paucity of data characterizing TEE in patients with cancer, current oncology
74 energy intake recommendations are based on an estimate of 25-30 kcal/kg body weight with a
75 call for further research (15). However, basing recommendations on body weight alone would
76 likely overestimate energy requirements in individuals with obesity and underestimate it in those
77 with low body weight (16). Furthermore, such recommendations do not consider body
78 composition, physical activity, cancer type, or disease stage, which might impact TEE.

79 The objectives of the current study were to compare TEE to current energy
80 recommendations and to characterize TEE in relation to body weight, body composition, and
81 physical activity. It was hypothesized that current energy recommendations would have poor
82 individual-level accuracy and TEE would differ according to body mass, body composition, and
83 PAL categories.

84 **Methods:**

85 *Study and subjects*

86 This analysis is part of a larger cross-sectional study measuring energy expenditure, body
87 composition, physical activity and dietary intake in patients with cancer (17). Patients with stage
88 II-IV CRC were recruited from the Cross Cancer Institute in Edmonton, Alberta, Canada. In line
89 with common practice in gastrointestinal oncology, patients with stage II or III CRC were
90 considered to have “early stage” disease. In addition, patients with lympho-vascular invasion, T4
91 tumor size, gastrointestinal obstruction, or high tumor grade were considered to have a high risk
92 for recurrence and were advised to undergo surgical removal of the tumor. Recruitment for the

93 full ongoing trial began in April 2016; between March 2017 and January 2018, patients were
94 offered additional TEE and body composition assessments. This study was approved by the
95 Health Research Ethics Board of Alberta and informed consent was obtained from all patients
96 prior to study assessments. Inclusion criteria were recent cancer diagnosis, aged 18-90 years, and
97 able to communicate freely in English. Exclusion criteria included anti-cancer therapy or surgery
98 within the past four weeks, confinement to a wheelchair, medications or conditions that might
99 affect body composition or metabolism (steroids, hormone replacement, unstable thyroid
100 disease), inability to breathe under the calorimetry hood for 30 minutes, pregnancy, or
101 breastfeeding. All measurements were completed within (before or after) two weeks of starting
102 anti-cancer therapy, where applicable.

103 *Patient-reported measures*

104 Individuals in this study were asked to complete several profiling questionnaires. Patients
105 completed the Patient-Generated Subjective Global Assessment (PG-SGA) – short form (18),
106 which consists of four sections: weight (score range: 0 – 5), food intake (score range: 0 – 4)
107 symptoms (score range: 0 – 24), and activities and function (score range: 0 – 3). Lower scores
108 indicate better results in each section. The European Organization for the Research and
109 Treatment of Cancer Quality of Life Questionnaire – C30 (version 3.0) (19) was also completed;
110 only overall quality of life score (range: 1 – 7) was used in this analysis, with higher scores
111 representing better quality of life. The International Physical Activity Questionnaire – Long
112 Form (IPAQ) (20) was used to measure subjective physical activity; continuous values from the
113 IPAQ were expressed as metabolic equivalencies of tasks (MET) minutes/week.

114 *Anthropometry and body composition*

115 Height and weight were measured using a Health-O-Meter Professional digital scale with
116 height rod (McCook, IL, USA; model number: 597KL) with shoes and heavy clothing removed.
117 One-month and six-month previous weight change percent was collected from the PG-SGA.
118 Body mass index (BMI) was calculated [weight (kg)/height (m²)] and classified according to the
119 World Health Organization's cut-points (21).

120 Body composition was assessed by dual X-ray absorptiometry (Lunar iDXA, GE
121 Healthcare, Chicago, IL; Encore 2001 software version 13.60) within a median 9 (IQR: 7 -14)
122 days of energy expenditure assessments. Fat mass (FM) and fat-free mass (FFM) were expressed
123 adjusting for height in m² (fat mass index, FMI, and fat-free mass index, FFMI) and as a ratio
124 (FM:FFM), to represent metabolic load and capacity as explained elsewhere (22). Percent body
125 fat was also reported. Appendicular skeletal muscle index (ASMI) was calculated as the sum of
126 lean soft tissue from limbs divided by height (kg/m²), with low ASMI defined as <5.45 kg/m² for
127 females and <7.26 kg/m² for males (23). Similarly, FFMI <15 kg/m² for females and <16 kg/m²
128 for males were used to define "myopenia" for exploratory purposes (24).

129 *Resting energy expenditure*

130 An indirect calorimeter with ventilated hood system (VMaxTM Spectra 29N, Nutritional
131 Assessment Instrument; Sensor-Medics, Yorba Linda, CA, USA) was used to measure REE.
132 This particular system is considered one of the most accurate metabolic carts (25) and has been
133 used as a gold standard in previous studies (26,27). Volume and air flow were calibrated prior to
134 each measurement using a three-liter syringe. Gas analysers were calibrated before each test with
135 standard gas concentrations of 20.95% oxygen (O₂) and 0.03% carbon dioxide (CO₂). Fraction of
136 expired carbon dioxide was kept between 0.75 and 0.80 for as much time as possible. Breath
137 samples were collected for 30 minutes and only steady state data (variations in volume of O₂ and

138 CO₂ of $\leq 10\%$ over five consecutive minutes) was used. The abbreviated Weir equation (28) was
139 used to calculate REE. Respiratory quotient was calculated as the ratio between carbon dioxide
140 produced and oxygen consumed (CO₂/O₂). Measured REE was compared to predicted REE to
141 identify high or low REE, or hyper- or hypo-metabolism, respectively. The Mifflin St.-Jeor
142 equation was used for predicted REE since it predicts REE with the most accuracy (29).

143 *Total energy expenditure*

144 TEE was the primary outcome of this investigation and was assessed using DLW over 14
145 days. Stock doses were formulated using 10 atom% oxygen 18 (¹⁸O) and 99.9 atom% deuterium
146 (²H) based on 1g/kg ¹⁸O and 0.1 g/kg ²H of body weight per patient. A single baseline urine
147 sample was collected before dosing (pre-dose). Patients drank the dose with a straw followed by
148 ~50mL tap water to rinse the dose cup; actual dose was therefore assumed to be the same as the
149 dose given. All patients were asked to collect a urine sample 4.5 and 6 hours after dosing and 1-2
150 times/day for the following 13 days. Only isotope enrichments from urine samples from pre-
151 dose, 4.5 and 6 hours post-dose, days 3, 7, and 14 were analyzed.

152 Measurement of ²H₂ and ¹⁸O isotope enrichments from stock doses and urine samples
153 were analyzed by using a dual inlet chromium reduction and continuous flow isotope ratio mass
154 spectrometer at the National Institutes of Health (Bethesda, MD, USA). Natural logarithms of ²H
155 and ¹⁸O enrichments were regressed against time, with slopes of regression lines representing
156 rates of ²H and ¹⁸O loss from body water (k_H and k_O , respectively). ²H and ¹⁸O dilution spaces
157 (N_H and N_O , respectively) were determined by dividing administered isotopes (in moles) by the
158 intercepts. Total body water was then calculated as (30,31):

159

160 Total body water = $0.5 \times (N_O/c_O + N_H/c_H)$

161

162 Where c_H and c_O were the sizes of 2H and ^{18}O pool sizes relative to total body water. To account
 163 for some isotopes entering organic pools, non-aqueous c_H was assumed to be 1.041 and c_O was
 164 assumed to be 1.007. The isotope fractionation for 2H leaving the body as water vapor is 0.946
 165 times the true rate of water it equilibrates with and the fractionation factor for ^{18}O leaving the
 166 body as CO_2 is 1.038 times the true rate of carbon dioxide production (32). We assumed breath
 167 was saturated with water vapor and non-sweat skin water vapour loss was proportional to
 168 exposed skin surface; therefore the simplified equation from the International Atomic Energy
 169 Agency (32) was used to calculate CO_2 as follows:

170

$$171 \text{ CO}_2 \text{ (moles)} = 0.455 \times \text{total body water} (c_O k_O - c_H k_H)$$

172

173 CO_2 was used in the modified Weir equation to calculate TEE as:

174

$$175 \text{ TEE (kcal/day)} = 22.4 \times (1.1 \times \text{CO}_2 + 3.9 \times \text{O}_2)$$

176

177 where O_2 (in liters/day) was calculated by:

178

$$179 \text{ O}_2 = \text{CO}_2 \div \text{food quotient}$$

180

181 Food quotient was assumed to be 0.86, representative of a typical diet on a population level (33).

182 Quality control measures to screen for unacceptable estimates included confirming the

183 following for each patient: ^{18}O enrichment/intercept >0.08 , linear fit of 2H and ^{18}O slopes, k_O/k_H

184 1.1 – 1.7, similar residuals of predicted and measured ^2H and ^{18}O , and $N_{\text{H}}/N_{\text{O}}$ 1.0 - 1.7. One
185 patient provided urine samples for isotope analysis on days 11 and 17 and both were assessed.
186 Another patient underwent unexpected surgery on day 5 and had 4 days of samples; since all
187 quality control measures outlined above were met (including $k_{\text{O}}/k_{\text{H}}=1.315$ and $N_{\text{H}}/N_{\text{O}}=1.050$)
188 and our results were similar with and without this patient, the data was kept in the final analyses.

189 TEE was expressed as kcal/day and kcal/kg body weight measured at the study visit
190 (same day as isotopic dosing and REE measurement). Predicted TEE was calculated as 25kcal/kg
191 and 30 kcal/kg body weight based on internationally-accepted clinical oncology guidelines from
192 the European Society for Clinical Nutrition and Metabolism (15) and from Dietary Reference
193 Intakes (DRI)(34), using the overweight and obese specific equation where appropriate. For
194 exploratory purposes, IPAQ categories were used to determine physical activity categories for
195 the DRI TEE equation as follows: sedentary: IPAQ category 1, low active: IPAQ category 2,
196 active: IPAQ category 3.

197 *Physical activity*

198 Physical activity level (PAL) was determined as the ratio between TEE and REE. Since
199 PAL is a ratio method and subject to bias as the regression intercept is not zero (35) (or could be
200 indicative of a non-linear relationship), activity was also expressed as residual activity-related
201 energy expenditure (RAEE) (36). This was calculated as the residual from TEE (dependent) and
202 REE (independent), with positive values being associated with higher-than-average physical
203 activity and negative numbers being associated with lower-than-average physical activity
204 (expressed in kcal/day).

205 Patients were asked to wear ActiCal accelerometers (Phillips Respironics, Bend, OR,
206 USA) during the 14-day collection period on the right hip. A 15-second epoch length was used.

207 Patients were also asked to keep a record of wear times, including time awoken in the morning
208 and time to bed in the evening. A valid day of monitoring was defined as ≥ 12 hours of wear time
209 (37). Only patients with at least four valid days of accelerometer monitoring were included (38).
210 TEE calculations from ActiCal was also compared to measured TEE.

211 *Medical variables*

212 At the time of assessment, patients were scheduled to begin either radiation,
213 chemotherapy, combined radiation and chemotherapy, or surveillance. Neutrophil to lymphocyte
214 ratio from medical records was used as a measure of systemic inflammation; only the value
215 closest to the study date was assessed in a cross-sectional manner. Prospective weight change
216 over treatment or surveillance was also acquired from medical records and expressed as %weight
217 change/100 days to account for varying follow-up appointment dates.

218 *Statistical analysis*

219 All data was assessed using SPSS software, version 24 (IBM Corp., Armonk, NY, USA),
220 with the threshold for significance set at $p \leq 0.05$. Normality in variables was determined using
221 the Shapiro-Wilk test. Non-normally distributed variables were reported as median and
222 interquartile range (IQR); otherwise, values are expressed as mean \pm SD. Effect size for post-hoc
223 sample size analysis was calculated using TEE data (n=12) at baseline from an ongoing clinical
224 trial in a similar population (39). An effect size of 0.73 and α 0.05 yielded a power of 0.89 to
225 detect a mean difference of 246 ± 334 kcal/day between measured versus predicted TEE from
226 the DRI intake recommendation using two-tailed paired samples t-test.

227 Pearson correlation coefficients or Spearman's rank-order correlation (for non-parametric
228 variables) described relationships between variables. BMI and PAL were split by the sample
229 median and FM:FFM was split by sex-specific sample median to explore differences in energy

230 expenditure. Paired t-tests assessed differences in parameters within individuals. Independent
231 samples t-tests or Mann-Whitney U-test (when dependent variables were non-normally
232 distributed for each group of the independent variable) determined differences between patient
233 groups stratified by sex, previous radiotherapy (yes or no), % REE from predicted, ASMI, PAL
234 median, RAEE (negative versus positive residuals), BMI median, sex-specific FM:FFM median,
235 or TEE. Bland-Altman analyses were used to assess the agreement between measured and
236 predicted TEE from current energy intake recommendations and ActiCal-derived TEE. Bias
237 indicates group-level agreement and is the mean difference between predicted minus measured
238 values. Limits of agreement, or bias \pm 1.96 SD, indicates agreement for each individual. Bias and
239 limits of agreement were expressed as percent to account for body size and individual energy
240 expenditure. Proportional bias was quantified by Pearson correlation coefficient between mean
241 of measured and predicted TEE and bias were used to determine if there were trends in the
242 magnitude of bias with increasing TEE.

243 **Results**

244 *Patients*

245 Between March 1, 2017 and January 31, 2018, 143 patients with CRC were approached
246 to participate, with 49 completing REE measurements (39.8% overall accrual). Of those, a total
247 of 21 patients (14 male) completed the optional doubly labeled water assessments (42.8% accrual
248 of those who completed basic study measurements), with 20 completing body composition and
249 accelerometer measurements, **Supplementary Figure 1**. Patient characteristics are presented in
250 **Table 1**. Only one patient had stage IV disease and was not an outlier in terms of energy
251 expenditure or body composition measurements. All other patients had stage II (n=3, 14.3%) or
252 stage III (n=17, 80.1%) disease and most individuals presented with overweight (n=8, 38.1%) or

253 obesity (n=8, 38.1%). Mean previous one-month weight change was $-1.5\% \pm 3.4\%$ (range: -
254 7.9%, 4.9%) and previous six-month weight change was $-5.3\% \pm 5.1\%$ (range: -20.0%, 0%),
255 with no differences in weight loss between sexes. Seven patients had weight loss $>5\%$ in the past
256 6 months. Four patients had undergone neoadjuvant combined radiotherapy and chemotherapy
257 (>1 month prior to study inclusion), with two having colon cancer and two having rectal cancer.
258 There were no differences in anthropometric, demographic, energy expenditure (including PAL),
259 or body composition variables between those who had received or not received radiotherapy.
260 Most (n=17) patients had undergone surgery for early stage high risk disease before (n=10,
261 median 49 days [IQR: 45 - 65 days] from study visit) or after (n=7, median 102 days [IQR: 95 -
262 102 days]) the study visit. Since many individuals will experience recurrence after curative
263 treatment (40) due to the presence of microscopic residual disease after surgery, individuals in
264 this study were still considered as patients with cancer after surgical resection. Most (n=10,
265 47.6%) were scheduled to undergo adjuvant chemotherapy with folinic acid, fluorouracil, and
266 oxaliplatin, with remaining patients scheduled to begin neoadjuvant radiochemotherapy (n=8,
267 38.1%), neoadjuvant short-course radiotherapy (n=2, 9.5%), or surveillance (n=1, 4.8%).

268 *Patient-reported measures*

269 Most patients had low scores for all PG-SGA boxes, indicating good nutritional status
270 and physical function. Most (n=11, 52.4%) scored 0 for weight change. All patients scored 0
271 (n=9, 42.9%) or 1 (n=12, 57.1%) for food intake. Symptom score was variable (range: 0, 6), with
272 most (n=13, 61.9%) indicating no symptoms. Within activities and function, most patients
273 indicated they were “normal with no limitations” (n=10, 47.6%) or “not my normal self, but able
274 to be up and about with fairly normal activities” (n=9, 42.9%), with two (9.5%) selecting “able to
275 do little activity and spend most of the day in bed or chair”. Median global quality of life score

276 was 75 (IQR: 58.3, 83.3), corresponding to median 5.5 (IQR: 4.5, 6.0) on a scale of 1 to 7. Self
277 reported physical activity from IPAQ was highly variable: median walking MET-minutes/week
278 was 693 (IQR: 396, 2871) and median moderate activity was 900 MET-minutes/week (IQR: 300,
279 1875). Most (n=17, 81.0%) did not report vigorous activity. Median total reported MET-
280 minutes/week was 1955 (IQR: 1265, 5724).

281 *Anthropometrics and body composition*

282 Anthropometric and body composition variables are presented in **Table 1**. As expected,
283 FFM and FFMI were lower in females; however, there were no differences in FM or FMI
284 between sexes. Median BMI was 28.7 kg/m² and median FM:FFM was 0.44 in males and 0.63 in
285 females.

286 *Energy expenditure description*

287 All measures of TEE from DLW met quality control estimates. Mean tracer elimination
288 rate (k_O/k_H) from DLW was normal (1.281 ± 0.050) and $^2\text{H}_2\text{:}^{18}\text{O}$ distribution volume (N_H/N_O) was
289 1.036 ± 0.018 . Males had higher REE and TEE, but not PAL, **Table 1**. Group median REE was
290 1698 kcal/day (IQR: 1146, 2009 kcal/day; mean \pm SD: 1764 ± 415 kcal/day), which was higher
291 than the Mifflin St.-Jeor prediction (median [IQR]: 1545 [1411, 1817], $P = 0.001$).

292 Approximately half (n=11, 52.4%) of patients had hypermetabolism and none had measured
293 REE <90% of predicted (suggestive of hypometabolism). Patients with hypermetabolism had
294 lower PAL (1.31 ± 0.22 vs. 1.56 ± 0.26 , $P = 0.024$) and RAEE (-179 ± 318 vs. 196 ± 373
295 kcal/day from the regression line, $P = 0.022$). However, percent REE bias was not correlated to
296 TEE in kcal/day or kcal/kg/day and there were no differences in TEE, percent previous one-
297 month or six-month weight change between groups; in other words, higher than “expected” REE

298 was associated with lower physical activity but did not relate to total energy requirements or
299 weight change.

300 Characteristics of TEE and PAL are presented in Table 1. A wide variability in TEE
301 expressed as kcal/day (range: 1562, 3622) and kcal/kg body weight/day (range: 20.4, 48.5) was
302 observed. Males had higher absolute TEE than females, although TEE in kcal/kg body weight
303 and PAL were not different between sexes. Approximately half (n=12, 57.1%) of patients fell
304 within 25-30 kcal/kg body weight, **Figure 1**. Mean PAL was 1.43 ± 0.27 (median:1.49) and was
305 also variable, ranging from 1.04 to 2.16.

306 Relationships between energy expenditure variables and age, body weight, FM, and FFM
307 are shown in **Table 2**. REE and TEE were positively correlated to body weight and FFM, with
308 higher correlations observed with FFM compared to body weight. PAL and RAEE were not
309 related to any variable. Four patients had low ASMI (all male) and two of these had weight loss
310 >2% in the previous 6 months (i.e. cachectic). There were no differences in any anthropometric,
311 energy expenditure, or physical activity variables between individuals with low versus normal
312 ASMI; these results were the same when only males were assessed. Similarly, only one patient
313 had FFMI below pre-defined cut-off values, precluding any further comparison.

314 *Agreement with energy recommendation estimations*

315 Energy recommendations were correlated with measured TEE in all equations ($r: 0.548 -$
316 0.826 , $p: 0.010 - <0.001$). Predicted energy recommendation with 25 kcal/kg was lower than
317 measured TEE (2128 ± 459 vs. 2473 ± 499 kcal/day, $P = 0.002$), but all other estimations were
318 not different on a group level, **Table 3**. However, less than half of patients had TEE within 10%
319 of all recommendations. Wide limits of agreement were also observed between TEE and all
320 energy recommendations; for example, even the recommendation with the smallest limits of

321 agreement (DRI with measured PAL) under-predicted by up to 22.5% below (484 kcal/day) to
322 22.7 % above (468 kcal/day) measured TEE, **Figure 2**. Using assumed PAL from IPAQ
323 categories did not improve the prediction ability and produced the widest limits of agreement (-
324 33.5, 50.2%, or -742, 1060 kcal/day). No proportional bias was apparent in any recommendation.

325 Body weight, FM, and FM:FFM were positively correlated to percent bias using 25
326 kcal/kg and 30 kcal/kg, **Table 4**. PAL and RAEE were negatively correlated to percent bias
327 from 25 kcal/kg, 30 kcal/kg, DRI with assumed PAL, and ActiCal TEE. Mean percent bias using
328 25 kcal/kg and 30 kcal/kg was lower (i.e. underestimation) in those with BMI and FM:FFM
329 below the medians (BMI median: 28.29 kg/m²; FM:FFM median: males: 0.44, females: 0.63),
330 **Figure 3**. Bias was frequently lower in those with higher PAL and RAEE, Figure 3. Patients
331 with TEE > 30 kcal/kg (n=7) had lower BMI (24.1 ± 3.3 vs. 30.4 ± 4.2 kg/m², $P < 0.001$), higher
332 PAL (1.67 ± 0.23 vs. 1.31 ± 0.20, $P = 0.001$), and higher RAEE (309 ± 387 vs. -154 ± 291
333 kcal/day, $P = 0.006$). REE bias from Mifflin St.-Jeor equations was not related to bias from TEE
334 equations.

335 *Activity patterns*

336 Mean wear time of the ActiCal devices was 12 ± 3 days, with 20 patients having ≥ 4 days
337 of wear time and at least one weekend (2 days) available. Total IPAQ score was not correlated to
338 any measure of energy expenditure and no other correlations between activity and body
339 composition, physical function, or quality of life was observed.

340 *Clinical parameters*

341 Mean weight change during treatment was -2.4 ± 5.2%/100 days and was not associated
342 with any energy expenditure, body composition, or physical activity variables. Mean neutrophil

343 to lymphocyte ratio was 3.4 ± 2.2 with a range of 1.29 to 9.33 and was also not associated with
344 any other variable.

345 **Discussion**

346 This study is the first to measure TEE in free living conditions in patients with primarily
347 earlier stage CRC. TEE and PAL were higher than previously reported and were greatly
348 variable. Current energy intake recommendations (15,34) did not reflect TEE in this cohort. Such
349 discrepancies were due to highly variable body composition and PAL, the latter of which cannot
350 accurately be estimated by patient recall.

351 As screening and treatment modalities continue to improve, it is expected that more
352 patients will be diagnosed at earlier stages of cancer with longer expected survival; therefore,
353 understanding differences in energy requirements in different cohorts of patients (i.e. early
354 versus late stages or by cancer type) is important for optimal nutritional care. However, our
355 current knowledge relies primarily on patients with cachexia and/or advanced disease, which
356 might be unrepresentative of many patients with CRC. The largest study to date that objectively
357 measured TEE using DLW included 24 cachectic patients with advanced pancreatic cancer who
358 had a mean BMI of 20 kg/m^2 and 19% pre-illness weight loss (7). Mean REE was higher and
359 TEE was lower than predicted; mean \pm SD PAL was 1.24 ± 0.20 at baseline. Others have
360 reported overall low PAL (8) and TEE (6) and that structured exercise can increase TEE (9) in
361 sample sizes ranging from four to eight patients with various cancer types. Mean PAL of our
362 sample was 1.43 ± 0.27 , which is higher than previously reported in oncology (7,8); this value
363 corresponds to a “low active” lifestyle (34) and is slightly lower than reported in healthy
364 individuals (PAL 1.6) (41). Compared to previous research (6,7), patients in the current sample
365 had generally earlier stage disease, less weight loss, lower incidence of low ASMI and low

366 FFMI. Notably, CRC is associated with lower incidence of weight/loss cachexia compared to
367 other cancer types (e.g. pancreatic, lung, gastric cancer) (42). Most individuals in this study also
368 had adequate physical function and PAL was highly variable. In advanced, cachectic patients,
369 higher REE and lower TEE may indicate an adaptive response to narrow the gap between TEE
370 and reduced energy intake or a reflection of low physical activity secondary to the disease and its
371 associated side effects (7), which may not occur in earlier stage CRC. Our findings are novel and
372 suggest that energy metabolism - and therefore energy requirements - differs greatly according to
373 cancer site and stage. Further exploration of the determinants of TEE and PAL according to
374 cancer site and stage is warranted.

375 We found that energy intake recommendations based on body weight alone were poor
376 assessments of actual energy requirements (assumed to be equal to TEE), with individual
377 differences ranging from -1613 kcal/day (or 48.5%) underprediction with 25 kcal/kg body
378 weight/day to 968 kcal/day (or 46.9%) overprediction with 30 kcal/kg body weight/day..
379 Additionally, a small proportion of energy requirement predictions fell within 10% of measured
380 TEE, ranging from 33.3% using 25 kcal/kg/day to 47.6% using DRI with measured PAL and
381 DRI with assumed PAL. This proportion is smaller than previous reports in healthy adults (62.9 -
382 85.7%)(43,44), suggesting that cancer impacts TEE in ways not captured by current energy
383 recommendations.

384 We found that bias using body weight-based equations was positively related to body
385 weight and composition (i.e. higher body weight, FM, and higher FM:FFM related to over-
386 prediction). Since obesity is a risk factor for several cancers (including CRC) (45,46), a large
387 number of individuals have obesity at diagnosis (47). However, low FFM is apparent at
388 diagnosis independent of body weight and FM and is not a condition exclusive to advanced

389 cancer (2). Energy recommendations might therefore have widespread error within oncology,
390 although further research in other populations is required.

391 While previous research suggests that TEE might be lower in the presence of high REE
392 (7), this was not apparent in the current study. Assuming an altered TEE based on REE alone or
393 by applying a universal activity and/or energy factor to measured or estimated REE likely
394 introduces substantial bias in energy recommendations. Several previous studies have
395 investigated REE in patients with CRC (48–52) or mixed tumor types (53,54). However, many
396 of these were limited in their interpretation of REE in relation to body composition since REE
397 was often divided by measures of muscularity (e.g. FFM), which creates a statistical bias
398 wherein smaller individuals will appear to have higher REE per kilogram of FFM (i.e. patients
399 with low body weight or cachexia might have an artificially high REE), as we (55) and others
400 (56–58) have discussed. Nevertheless, these studies collectively suggest that REE and body
401 composition might differ according to tumor site (53,59,60) and relates to cancer stage and
402 systemic inflammation (51,61). While neutrophil:lymphocyte was not associated with energy
403 metabolism in the present analyses, more sensitive indices of systemic inflammation (i.e. C-
404 reactive protein, interleukin-6, tumor necrosis factor- α) might relate to TEE and PAL and should
405 be investigated in more depth. The current study builds upon this line of investigation and
406 provides new evidence that body composition and physical activity might also relate to energy
407 requirements to a greater degree than “high” REE. Equations that incorporate body composition
408 and physical activity and that are developed from oncology populations would likely be more
409 accurate, although further research on the feasibility and accuracy of such approaches is needed.

410 Physical activity is highly variable in healthy individuals and can significantly impact
411 TEE. In the present study, PAL variability was similar than that of sedentary to lightly-active

412 healthy adults (34,62). According to our data, it appears that physical activity also greatly
413 impacted energy requirements in these patients and was the most variable component of TEE.
414 However, subjective measures of physical activity (IPAQ) did not improve estimation of energy
415 requirements and were not related to any physical or clinical measure. This is likely because
416 physical activity is often over- or under-reported (63,64) and is therefore a poor reflection of
417 actual physical activity engagement. Since physical activity is feasible, safe, and beneficial for
418 patients with cancer (65–67) and impacts energy requirements, improved techniques for
419 capturing this modality are needed.

420 While this is the largest exploratory study of TEE in earlier stage cancer and CRC using
421 several accurate techniques, there are inherent limitations. Firstly, DLW measures TEE over a
422 span of only two weeks. The impact of anti-cancer therapy (and associated side effects), body
423 composition changes, or disease progression on TEE and physical activity patterns cannot be
424 assumed, but should be investigated in more depth. Although our sample size was sufficient to
425 detect differences in predicted and measured TEE from the DRI equation, the variability in
426 equation error should be confirmed in samples with larger numbers of individuals and with
427 different tumor types (as energy metabolism might presumably vary in this regard).

428 In conclusion, TEE and physical activity were highly variable in patients with CRC,
429 which was not apparent in current energy recommendations on an individual level. TEE differed
430 according to categories of body weight, body composition, and physical activity; these variables
431 also impacted error associated with energy recommendations. Future research should therefore
432 characterize the feasibility and impact of incorporating body composition and physical activity in
433 the estimation of energy requirements for patients with cancer.

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440

441 **Conflict of interest:** None.

442

443 The authors contributions were as follows: CMP and SAP conceptualized the study. SAP, SAE,
444 PJW, TP, HC, MBS, and CMP were responsible for research design; SAP conducted research
445 and analyzed data; all authors (SAP, SAE, PJW, TP, HC, RJES, MBS, CMP) contributed to data
446 interpretation; PJW and HC provided essential materials; SAP and CMP wrote paper and had
447 primary responsibility for final content. All authors read and approved the final manuscript.

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Table 1. Characteristics of 21 patients with colorectal cancer¹

Characteristic	Total (n=21) ²	Males (n=14)	Females (n=7)	P value ³
Age, years	57 ± 12 (34 – 73)	55 ± 13 (34 – 72)	59 ± 13 (40 – 73)	0.582
Body weight, kg	85.1 ± 18.4 (54.3 – 131.1)	91.5 ± 17.3 (68.6 – 131.1)	72.5 ± 14.0 (54.3 – 92.6)	0.021
Body mass index, kg/m ²	28.3 ± 4.9 (20.9 – 39.5)	29.2 ± 4.9 (20.9 – 39.5)	26.7 ± 4.9 (22.0 – 35.0)	0.294
Fat mass, kg	28.8 ± 12.3 (9.9 – 59.8)	29.5 ± 13.8 (9.9 – 59.8)	27.6 ± 9.6 (16.5 – 41.4)	0.754
Fat mass index, kg/m ²	9.6 ± 3.8 (3.1 – 18.0)	9.3 ± 3.8 (3.1 – 18.0)	10.1 ± 3.4 (6.3 – 15.1)	0.651
Percent fat	32.9 ± 8.7 (14.7 – 45.6)	30.6 ± 9.1 (14.7 – 45.6)	37.3 ± 6.3 (27.6 – 44.4)	0.101
Fat-free mass, kg	56.3 ± 10.7 (37.6 – 74.1)	62.6 ± 6.8 (48.1 – 74.1)	44.6 ± 5.1 (37.6 – 51.8)	<0.001
Fat-free mass index, kg/m ²	18.6 ± 2.4 (14.1 – 22.2)	19.8 ± 1.8 (16.5 – 22.2)	16.5 ± 1.9 (14.1 – 19.8)	0.001
Fat mass:fat-free mass	0.51 ± 0.19 (0.17 – 0.84)	0.46 ± 0.19 (0.17 – 0.84)	0.61 ± 0.16 (0.38 – 0.80)	0.102
Appendicular skeletal muscle, kg	24.4 ± 6.4 (16.2 – 42.6)	27.5 ± 5.6 (20.3 – 42.6)	18.5 ± 2.1 (16.2 – 21.4)	0.001
Appendicular skeletal muscle index, kg/m ²	7.9 ± 1.5 (5.7 – 12.3)	8.5 ± 1.5 (6.9 – 12.3)	6.9 ± 0.9 (5.7 – 8.4)	0.018
Resting energy expenditure, kcal/day	1698 (IQR: 1446 – 2009)	1841 (IQR: 1668 – 2077)	1423 (IQR: 1388 – 1500)	<0.001
Respiratory quotient	0.80 ± 0.05 (0.73 – 0.93)	0.81 ± 0.05 (0.73 – 0.93)	0.79 ± 0.03 (0.74 – 0.82)	0.393
Total energy expenditure, kcal/day	2473 ± 499 (1562 – 3622)	2646 ± 490 (1929 – 3622)	2127 ± 313 (1562 – 2509)	0.020
Total energy expenditure, kcal/kg body weight	29.7 ± 6.3 (20.4 – 48.5)	29.7 ± 7.1 (20.4 – 48.5)	29.8 ± 4.8 (25.1 – 36.1)	0.952
Physical activity level	1.43 ± 0.27 (1.04 – 2.16)	1.40 ± 0.29 (1.04 – 2.16)	1.49 ± 0.22 (1.04 – 1.76)	0.463

¹Presented as mean ± SD (range) or median (interquartile [IQR] range) for non-normality between groups. Physical activity level is total energy expenditure:resting energy expenditure.

²n=20 total and n=13 males with body composition measurements

³All differences tested using independent samples t-test except in the case of non-normality wherein Mann-Whitney U-test was utilized.

Table 2. Correlations between energy expenditure, demographic and body composition variables (n=21)¹

	Age	Weight	FM	FFM	FM:FFM
Resting energy expenditure²	-0.353	0.729*	0.388	0.873*	-0.029
Total energy expenditure	-0.382	0.558*	0.350	0.658*	0.025
Physical activity level	0.163	-0.366	-0.396	-0.255	-0.273
RAEE	0.083	0.050	-0.093	0.213	-0.197

¹Numbers are r values. * $P < 0.05$, correlation. FM:FFM: fat mass:fat-free mass; RAEE: residual activity energy expenditure (residual from total energy expenditure and resting energy expenditure)

²Spearman's rank-order correlation; all other values derived from Pearson correlation

Table 3. Agreement between measured and estimated total energy expenditure (TEE) (n=21)¹

	Mean \pm SD, kcal/day	Percent bias, mean \pm SD	Proportional bias ²		LOA, %	Absolute LOA, %	Minimum difference, %	Maximum difference, %	Within 10% measured TEE, n (%)
			<i>r</i>	<i>P</i>					
Measured TEE	2473 \pm 499								
25 kcal/kg	2128 \pm 459*	-12.6 \pm 16.5	-0.099	0.670	-45.1, 19.8	64.9	-48.5	22.4	7 (33.3)
30 kcal/kg	2554 \pm 551	4.8 \pm 19.9	0.120	0.604	-34.1, 43.8	77.8	-38.2	46.9	8 (38.1)
DRI – measured PAL	2554 \pm 495	4.1 \pm 12.9	-0.012	0.958	-21.2, 29.3	50.5	-22.5	22.7	10 (47.6)
DRI – assumed PAL	2632 \pm 510	8.3 \pm 21.4	0.029	0.901	-33.5, 50.2	83.8	-22.5	48.9	10 (47.6)
ActiCal	2359 \pm 549	-4.6 \pm 19.5	0.125	0.600	-42.7, 33.6	76.3	-35.1	43.3	9 (42.9)

¹DRI, dietary reference intake; LOA, limits of agreement; PAL, physical activity level. * $P \leq 0.05$ difference between measured TEE and energy intake recommendations via paired samples t-test.

²Proportional bias determined as Pearson correlation between bias and mean of measured and predicted TEE.

Table 4. Correlation of percent bias between total energy expenditure and estimations with patient characteristics (n=21)¹

	Age	Weight	FM	FFM	FM:FFM	PAL	RAEE
25 kcal/kg	0.133	0.509*	0.586*	0.285	0.507*	-0.767*	-0.722*
30 kcal/kg	0.133	0.509*	0.586*	0.285	0.507*	-0.767*	-0.722*
DRI – measured PAL	-0.240	-0.008	-0.225	0.245	-0.410	-0.344	-0.384
DRI – assumed PAL	-0.194	0.187	0.084	0.290	-0.085	-0.791*	-0.760*
ActiCal	-0.107	0.478*	0.429	0.380	0.297	-0.631*	-0.587*

¹Percent bias calculated as (energy intake recommendation - total energy expenditure / total energy expenditure) x 100.
FFM, fat-free mass; FM, fat mass; PAL, physical activity level; RAEE: residual activity energy expenditure (residual from total energy expenditure and resting energy expenditure)

* $P < 0.05$, Pearson correlation

Figure legends

Figure 1. Range of measured total energy expenditure (TEE) in kcal/kg body weight in 21 patients with colorectal cancer. Each point is a patient. The box represents current recommendations of 25-30 kcal/kg body weight from the European Society for Clinical Nutrition and Metabolism (Arends et al. Clin Nutr. 2017; 36[5]:1187-96) (15).

Figure 2. Bland-Altman plots of measured versus predicted total energy expenditure (TEE) in 21 patients with colorectal cancer. The middle solid line represents bias (mean difference between measured and predicted TEE) and the two parallel dotted lines represent the 95% limits of agreement (bias \pm 1.96 SD). Proportional bias was determined as Pearson correlation coefficient between mean of measured and predicted TEE and bias; no proportional bias was apparent in any recommendation. DRI, dietary reference intakes; PAL, physical activity level, measured as TEE:resting energy expenditure. DRI was calculated using measured PAL and estimated from a subjective questionnaire.

Figure 3. Percent bias of predicted minus measured total energy expenditure according to median of body mass index (A), fat mass:fat-free mass (FM:FFM)(B), physical activity level (PAL)(C), and residual activity energy expenditure (RAEE)(D). * $p \leq 0.05$, independent samples t-test. aPAL, assumed PAL from subjective questionnaire; DRI, dietary reference intake; mPAL, measured physical activity level. N=21. Data are presented as mean \pm SEM.