Total energy expenditure in patients with colorectal cancer

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Abbreviations used: ^{2}H, 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

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Abstract

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

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

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

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

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

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

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

Introduction:

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

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

To date, only four reports have measured TEE in cancer using objective and accurate techniques such as doubly labeled water (DLW) or bicarbonate-urea (6–9), which severely limits current understanding of energy requirements in oncology settings. The majority of patients in these previous studies had advanced (i.e. stage IV) disease (6) or severe weight loss (i.e. 19% of pre-illness body weight)(7). However, this likely represents a small proportion of patients with certain types of cancer. For example, colorectal cancer (CRC) is the third most commonly diagnosed cancer in the World (10); improvements in screening practices, lower incidence of risk factors, and effective treatments options has led to a higher proportion of cancer cases diagnosed at earlier stages (11), where severe wasting/weight loss (i.e. cachexia (12)) and high systemic inflammation is less common (13). These patients also have a high prevalence of obesity at diagnosis and weight gain during curative-intent treatment (14).

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

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

Methods:

Study and subjects

This analysis is part of a larger cross-sectional study measuring energy expenditure, body composition, physical activity and dietary intake in patients with cancer (17). Patients with stage II-IV CRC were recruited from the Cross Cancer Institute in Edmonton, Alberta, Canada. In line with common practice in gastrointestinal oncology, patients with stage II or III CRC were considered to have “early stage” disease. In addition, patients with lympho-vascular invasion, T4 tumor size, gastrointestinal obstruction, or high tumor grade were considered to have a high risk for recurrence and were advised to undergo surgical removal of the tumor. Recruitment for the full ongoing trial began in April 2016; between March 2017 and January 2018, patients were offered additional TEE and body composition assessments. This study was approved by the Health Research Ethics Board of Alberta and informed consent was obtained from all patients prior to study assessments. Inclusion criteria were recent cancer diagnosis, aged 18-90 years, and able to communicate freely in English. Exclusion criteria included anti-cancer therapy or surgery within the past four weeks, confinement to a wheelchair, medications or conditions that might affect body composition or metabolism (steroids, hormone replacement, unstable thyroid disease), inability to breathe under the calorimetry hood for 30 minutes, pregnancy, or breastfeeding. All measurements were completed within (before or after) two weeks of starting anti-cancer therapy, where applicable.

Patient-reported measures

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

Anthropometry and body composition

Height and weight were measured using a Health-O-Meter Professional digital scale with height rod (McCook, IL, USA; model number: 597KL) with shoes and heavy clothing removed. One-month and six-month previous weight change percent was collected from the PG-SGA. Body mass index (BMI) was calculated [weight (kg)/height (m^2)] and classified according to the World Health Organization's cut-points (21).

Body composition was assessed by dual X-ray absorptiometry (Lunar iDXA, GE Healthcare, Chicago, IL; Encore 2001 software version 13.60) within a median and standard error of 9 ± 3 days of energy expenditure assessments. Fat mass (FM) and fat-free mass (FFM) were expressed adjusting for height in m^2 (fat mass index, FMI, and fat-free mass index, FFMI) and as a ratio (FM:FFM), to represent metabolic load and capacity as explained elsewhere (22). Percent body fat was also reported. Appendicular skeletal muscle index (ASMI) was calculated as the sum of lean soft tissue from limbs divided by height (kg/m^2), with low ASMI defined as $<5.45\ kg/m^2$ for females and $<7.26\ kg/m^2$ for males (23). Similarly, FFMI $<15\ kg/m^2$ for females and $<16\ kg/m^2$ for males were used to define "myopenia" for exploratory purposes (24).

Resting energy expenditure

An indirect calorimeter with ventilated hood system (VMax^{TM} Spectra 29N, Nutritional Assessment Instrument; Sensor-Medics, Yorba Linda, CA, USA) was used to measure REE. This particular system is considered one of the most accurate metabolic carts (25) and has been used as a gold standard in previous studies (26,27). Volume and air flow were calibrated prior to each measurement using a three-liter syringe. Gas analysers were calibrated before each test with standard gas concentrations of 20.95% oxygen (O_2) and 0.03% carbon dioxide (CO_2). Fraction of expired carbon dioxide was kept between 0.75 and 0.80 for as much time as possible. Breath samples were collected for 30 minutes and only steady state data (variations in volume of O_2 and

CO_2 of ≤ 10% over five consecutive minutes) was used. The abbreviated Weir equation (28) was used to calculate REE. Respiratory quotient was calculated as the ratio between carbon dioxide produced and oxygen consumed (CO_2/O_2). Measured REE was compared to predicted REE to identify high or low REE, or hyper- or hypo-metabolism, respectively. The Mifflin St.-Jeor equation was used for predicted REE since it predicts REE with the most accuracy (29).

Total energy expenditure

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

Measurement of $^{2}H_2$ and ^{18}O isotope enrichments from stock doses and urine samples were analyzed by using a dual inlet chromium reduction and continuous flow isotope ratio mass spectrometer at the National Institutes of Health (Bethesda, MD, USA). Natural logarithms of ^{2}H and ^{18}O enrichments were regressed against time, with slopes of regression lines representing rates of ^{2}H and ^{18}O loss from body water (k_H and k_O, respectively). ^{2}H and ^{18}O dilution spaces (N_H and N_O, respectively) were determined by dividing administered isotopes (in moles) by the intercepts. Total body water was then calculated as (30,31):

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

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

$$CO_2 \text{ (moles)} = 0.455 \text{ x total body water } (c_O k_O - c_H k_H)$$

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

$$\text{TEE (kcal/day)} = 22.4 \text{ x } (1.1 \text{ x } CO_2 + 3.9 \text{ x } O_2)$$

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

$$O_2 = CO_2 \div \text{food quotient}$$

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

Quality control measures to screen for unacceptable estimates included confirming the following for each patient: ^{18}O enrichment/intercept >0.08, linear fit of ^{2}H and ^{18}O slopes, k_O/k_H

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

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

Physical activity

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

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

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

Medical variables

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

Statistical analysis

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

Pearson correlation coefficients or Spearman's rank-order correlation (for non-parametric variables) described relationships between variables. BMI and PAL were split by the sample median and FM:FFM was split by sex-specific sample median to explore differences in energy expenditure. Paired t-tests assessed differences in parameters within individuals. Independent samples t-tests or Mann-Whitney U-test (when dependent variables were non-normally distributed for each group of the independent variable) determined differences between patient groups stratified by sex, previous radiotherapy (yes or no), % REE from predicted, ASMI, PAL median, RAEE (negative versus positive residuals), BMI median, sex-specific FM:FFM median, or TEE. Bland-Altman analyses were used to assess the agreement between measured and predicted TEE from current energy intake recommendations and ActiCal-derived TEE. Bias indicates group-level agreement and is the mean difference between predicted minus measured values. Limits of agreement, or bias ± two standard deviations, indicates agreement for each individual. Bias and limits of agreement were expressed as percent to account for body size and individual energy expenditure. Proportional bias was quantified by Pearson correlation coefficient between mean of measured and predicted TEE and bias were used to determine if there were trends in the magnitude of bias with increasing TEE.

Results

Patients

Between March 1, 2017 and January 31, 2018, 143 patients with CRC were approached to participate, with 49 completing REE measurements (39.8% overall accrual). Of those, a total of 21 patients (14 male) completed the optional doubly labeled water assessments (42.8% accrual of those who completed basic study measurements), with 20 completing body composition and accelerometer measurements, **Supplementary Figure 1**. Patient characteristics are presented in **Table 1**. Only one patient had stage IV disease and was not an outlier in terms of energy expenditure or body composition measurements. All other patients had stage II (n=3, 14.3%) or stage III (n=17, 80.1%) disease and most individuals presented with overweight (n=8, 38.1%) or obesity (n=8, 38.1%). Average previous one-month weight change was -1.5% ± 3.4% (range: -7.9%, 4.9%) and previous six-month weight change was -5.3% ± 5.1% (range: -20.0%, 0%), with no differences in weight loss between sexes. Seven patients had weight loss >5% in the past 6 months. Four patients had undergone neoadjuvant combined radiotherapy and chemotherapy (>1 month prior to study inclusion), with two having colon cancer and two having rectal cancer. There were no differences in anthropometric, demographic, energy expenditure (including PAL), or body composition variables between those who had received or not received radiotherapy. Most (n=17) patients had undergone surgery for early stage high risk disease before (n=10, median 49 days [IQR: 45 - 65 days] from study visit) or after (n=7, median 102 days [IQR: 95 – 102 days]) the study visit. Since many individuals will experience recurrence after curative treatment (40) due to the presence of microscopic residual disease after surgery, individuals in this study were still considered as patients with cancer after surgical resection. Most (n=10, 47.6%) were scheduled to undergo adjuvant chemotherapy with folinic acid, fluorouracil, and oxaliplatin, with remaining patients scheduled to begin neoadjuvant radiochemotherapy (n=8, 38.1%), neoadjuvant short-course radiotherapy (n=2, 9.5%), or surveillance (n=1, 4.8%).

Patient-reported measures

Most patients had low scores for all PG-SGA boxes, indicating good nutritional status and physical function. Most (n=11, 52.4%) scored 0 for weight change. All patients scored 0 (n=9, 42.9%) or 1 (n=12, 57.1%) for food intake. Symptom score was variable (range: 0, 6), with most (n=13, 61.9%) indicating no symptoms. Within activities and function, most patients indicated they were “normal with no limitations” (n=10, 47.6%) or “not my normal self, but able to be up and about with fairly normal activities” (n=9, 42.9%), with two (9.5%) selecting “able to do little activity and spend most of the day in bed or chair”. Median global quality of life score 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 reported physical activity from IPAQ was highly variable: median walking MET-minutes/week was 693 (IQR: 396, 2871) and median moderate activity was 900 MET-minutes/week (IQR: 300, 1875). Most (n=17, 81.0%) did not report vigorous activity. Median total reported MET-minutes/week was 1955 (IQR: 1265, 5724).

Anthropometrics and body composition

Anthropometric and body composition variables are presented in **Table 1**. As expected, FFM and FFMI were lower in females; however, there were no differences in FM or FMI between sexes. Median BMI was 28.7 kg/m^2 and median FM:FFM was 0.44 in males and 0.63 in females.

Energy expenditure description

All measures of TEE from DLW met quality control estimates. Mean tracer elimination rate (k_O/k_H) from DLW was normal (1.281 ± 0.050) and $^2H_2$:^{18}O distribution volume (N_H/N_O) was 1.036 ± 0.018. Males had higher REE and TEE, but not PAL, **Table 1**. Group median REE was 1698 kcal/day (IQR: 1146, 2009 kcal/day; mean ± standard deviation: 1764 ± 415 kcal/day), which was higher than the Mifflin St.-Jeor prediction (median [IQR]: 1545 [1411, 1817], P = 0.001). Approximately half (n=11, 52.4%) of patients had hypermetabolism and none had measured REE <90% of predicted (suggestive of hypometabolism). Patients with hypermetabolism had lower PAL (1.31 ± 0.22 vs. 1.56 ± 0.26, P = 0.024) and RAEE (-179 ± 318 vs. 196 ± 373 kcal/day from the regression line, P = 0.022). However, percent REE bias was not correlated to TEE in kcal/day or kcal/kg/day and there were no differences in TEE, percent previous one-month or six-month weight change between groups; in other words, higher than "expected" REE was associated with lower physical activity but did not impact total energy requirements or weight change.

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

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

Agreement with energy recommendation estimations

Energy recommendations were correlated with measured TEE in all equations (r: 0.548 – 0.826, p: 0.010 – <0.001). Predicted energy recommendation with 25 kcal/kg was lower than measured TEE (2128 ± 459 vs. 2473 ± 499 kcal/day, P = 0.002), but all other estimations were not different on a group level, **Table 3**. However, less than half of patients had TEE within 10% of all recommendations. Wide limits of agreement were also observed between TEE and all energy recommendations; for example, even the recommendation with the smallest limits of agreement (DRI with measured PAL) under-predicted by up to 22.5% below (484 kcal/day) to 22.7 % above (468 kcal/day) measured TEE, **Figure 2**. Using assumed PAL from IPAQ categories did not improve the prediction ability and produced the widest limits of agreement (-33.5, 50.2%, or -742, 1060 kcal/day). No proportional bias was apparent in any recommendation.

Body weight, FM, and FM:FFM were positively correlated to percent bias using 25 kcal/kg and 30 kcal/kg, **Table 4**. PAL and RAEE were negatively correlated to percent bias from 25 kcal/kg, 30 kcal/kg, DRI with assumed PAL, and ActiCal TEE. Average percent bias using 25 kcal/kg and 30 kcal/kg was lower (i.e. underestimation) in those with BMI and FM:FFM below the medians (BMI median: 28.29 kg/m^2; FM:FFM median: males: 0.44, females: 0.63), **Figure 3**. Bias was frequently lower in those with higher PAL and RAEE, Figure 3. Patients with TEE > 30 kcal/kg (n=7) had lower BMI (24.1 ± 3.3 vs. 30.4 ± 4.2 kg/m^2, P < 0.001), higher PAL (1.67 ± 0.23 vs. 1.31 ± 0.20, P = 0.001), and higher RAEE (309 ± 387 vs. -154 ± 291 kcal/day , P = 0.006). REE bias from Mifflin St.-Jeor equations was not related to bias from TEE equations.

Activity patterns

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

Average weight change during treatment was -2.4 ± 5.2%/100 days and was not associated with any energy expenditure, body composition, or physical activity variables. Average neutrophil to lymphocyte ratio was 3.4 ± 2.2 with a range of 1.29 to 9.33 and was also not associated with any other variable.

Discussion

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

As screening and treatment modalities continue to improve, it is expected that more patients will be diagnosed at earlier stages of cancer with longer expected survival; therefore, understanding differences in energy requirements in different cohorts of patients (i.e. early versus late stages or by cancer type) is important for optimal nutritional care. However, our current knowledge relies primarily on patients with cachexia and/or advanced disease, which might be unrepresentative of many patients with CRC. The largest study to date that objectively measured TEE using DLW included 24 cachectic patients with advanced pancreatic cancer who had an average BMI of 20 kg/m^2 and 19% pre-illness weight loss (7). Average REE was higher and TEE was lower than predicted; average PAL was 1.24 ± [standard error] 0.04 at baseline. Others have reported overall low PAL (8) and TEE (6) and that structured exercise can increase TEE (9) in sample sizes ranging from four to eight patients with various cancer types. Average PAL of our sample was 1.43 ± 0.27, which is higher than previously reported in oncology (7,8); this value corresponds to a “low active” lifestyle (34) and is slightly lower than reported in healthy individuals (PAL 1.6) (41). Compared to previous research (6,7), patients in the current sample had generally earlier stage disease, less weight loss, lower incidence of low ASMI and low FFMI. Notably, CRC is associated with lower incidence of weight/loss cachexia compared to other cancer types (e.g. pancreatic, lung, gastric cancer) (42). Most individuals in this study also had adequate physical function and PAL was highly variable. In advanced, cachectic patients, higher REE and lower TEE may indicate an adaptive response to narrow the gap between TEE and reduced energy intake or a reflection of low physical activity secondary to the disease and its associated side effects (7), which may not occur in earlier stage CRC. Our findings are novel and suggest that energy metabolism - and therefore energy requirements - differs greatly according to cancer site and stage. Further exploration of the determinants of TEE and PAL according to cancer site and stage is warranted.

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

We found that bias using body weight-based equations was positively related to body weight and composition (i.e. higher body weight, FM, and higher FM:FFM related to over-prediction). Since obesity is a risk factor for several cancers (including CRC) (45,46), a large number of individuals have obesity at diagnosis (47). However, low FFM is apparent at diagnosis independent of body weight and FM and is not a condition exclusive to advanced cancer (2). Energy recommendations might therefore have widespread error within oncology, although further research in other populations is required.

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

Physical activity is highly variable in healthy individuals and can significantly impact TEE. In the present study, PAL variability was similar than that of sedentary to lightly-active healthy adults (34,62). According to our data, it appears that physical activity also greatly impacted energy requirements in these patients and was the most variable component of TEE.

However, subjective measures of physical activity (IPAQ) did not improve estimation of energy requirements and were not related to any physical or clinical measure. This is likely because physical activity is often over- or under-reported (63,64) and is therefore a poor reflection of actual physical activity engagement. Since physical activity is feasible, safe, and beneficial for patients with cancer (65–67) and impacts energy requirements, improved techniques for capturing this modality are needed.

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

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

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Table 1. Characteristics of 21 patients with colorectal cancer[1]

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 ± 13.8 (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

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

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

[3]All 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 expenditure[2]	-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

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

[1]DRI, 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.
[2]Proportional 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*

[1]Percent 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 ± 2 standard deviations). 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 ± standard error of the mean.