Title:

Total energy expenditure assessed by 24-hour whole-room indirect calorimeter in patients with colorectal cancer: baseline findings from the PRIMe study

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Running Title: Energy requirements in cancer by room calorimeter

Abbreviations: ALST: appendicular lean soft tissue; BMI: body mass index; CRC: colorectal cancer; LST: lean soft tissue; REE: resting energy expenditure; TEE: total energy expenditure.

Data Sharing: Data described in the manuscript, code book, and analytic code will be made available upon request pending written application and approval.

Abstract

Background: Total energy expenditure (TEE) determines energy requirements, but objective data in patients with cancer is limited.

Objective: We aimed to characterize TEE, investigate its predictors, and compare TEE with cancer-specific predicted energy requirements.

Design: This cross-sectional analysis included patients with stage II-IV colorectal cancer from the Protein Recommendation to Increase Muscle (PRIMe) trial. TEE was assessed by 24-hour stay in a whole-room indirect calorimeter prior to dietary intervention and compared to cancer-specific predicted energy requirements (25-30 kcal/kg). Generalized linear models, paired samples t-tests, and Pearson correlation were applied.

Results: Thirty-one patients (56±10 years; BMI: 27.9±5.5 kg/m^2; 68% male) were included. Absolute TEE was higher in males (mean [95% CI] difference: 391 [167, 616] kcal/day; p<0.001), patients with colon cancer (279 [73, 485] kcal/day; p=0.010), and obesity (393 [-182, 604] kcal/day; p<0.001). Appendicular lean soft tissue (β [95% CI]: 46.72 [34.27, 59.17]; p<0.001) and tumor location (colon: 139.69 [19.44, 259.95]; p=0.023) independently predicted TEE when adjusted for sex. Error between measured TEE and energy requirements predicted by 25 kcal/kg (241 [76, 405] kcal/day; p=0.010) and 30 kcal/kg (367 [163, 571] kcal/day; p<0.001) was higher for patients with obesity, and proportional error was observed (25 kcal/kg: r = -0.587; p<0.001 and 30 kcal/kg: r = -0.751; p<0.001). TEE (25 kcal/kg; 95% CI: 24, 27 kcal/kg) was below predicted requirements using 30 kcal/kg (-430±322 kcal/day; p<0.001).

Conclusion: This is the largest study to assess TEE of patients with cancer by whole-room indirect calorimeter and highlights the need for improved determination of energy requirements in this population. Energy requirements predicted using 30 kcal/kg overestimated TEE by 1.44

times in a controlled sedentary environment and TEE was outside of the predicted requirement range for most. Special considerations are warranted when determining TEE of patients with colorectal cancer, including BMI, body composition and tumor location.

This is a baseline cross-sectional analysis from a clinical trial (ClinicalTrials.gov Identifier: NCT02788955) available at: https://clinicaltrials.gov/ct2/show/NCT02788955

Keywords: whole-room indirect calorimetry, whole-body indirect calorimetry, cancer, energy expenditure, energy requirements, body composition

Introduction

Total energy expenditure (TEE) determines energy requirements; thus accurate measurement of TEE is especially important in conditions that are associated with altered energy metabolism such as cancer. Energetic demands imposed by cancer vary by type and stage of disease and may influence resting energy expenditure (REE), the largest part of TEE (1). Other factors commonly observed in patients with cancer such as increased systemic inflammation (and downstream effects on oxidative stress and proteolysis) and changes in body composition may also impact energy expenditure, likely through skeletal muscle breakdown and the ubiquitin-proteasome pathways (2, 3). Skeletal muscle plays an important role as it is a storage site of glycogen and amino acids and is a regulator of energy expenditure, especially when other energy sources in the body are depleted (4). Despite the multitude of factors that may impact specific components of TEE in cancer, few studies have measured TEE using accurate tools in adults with cancer (5-7). Hence, current guidelines assume patients with cancer have TEE (and energy requirements) similar to healthy populations without cancer (8).

Energy requirements are often predicted in clinical settings by estimating REE and applying an activity factor or by directly predicting TEE (e.g., using 25-30 kcal/kg for patients with cancer (8)). However, the inter-individual accuracy of prediction equations in people with cancer is poor (5, 9). To better understand energy requirements and its determinants in people with cancer, accurate assessments of TEE are needed. One way to measure TEE in a controlled sedentary environment is through single- or multi-day stays in a whole-room indirect calorimeter. (10-12). This controlled setting allows for quantification of nitrogen intake (e.g., via nutrient intake analysis) and losses (e.g., via 24-hour urinary nitrogen) and the ability to control dietary intake. The whole-room calorimeter offers a controlled environment to rigorously assess determinants of TEE, especially in populations with low levels of physical activity, such as patients with cancer (5, 6), or those receiving ongoing treatment in a hospitalized setting. The enforced sedentary environment of room calorimeters can result in the underestimation of TEE when compared to free-living conditions, particularly for individuals who regularly engage in physical activities that are not captured during their stay in the room calorimeter (11). If individuals' typical level of physical activity is unaccounted for, TEE determined by room calorimeter may underestimate the energy requirements of individuals in free-living conditions, potentially resulting in unintentional weight loss.

Nevertheless, room calorimeters offer an opportunity to assess the influence of disease-specific factors (e.g., tumor location, cancer stage) on TEE in a controlled environment. The complexity and intricacies of room calorimeters are such that there are only approximately 45 centers globally known to house functioning units (10, 13); as such, their use in various clinical conditions is limited. The last known assessment of TEE by whole-room indirect calorimetry in patients with cancer was conducted in patients (n=5) with unresectable small-cell lung cancer >25 years ago (7).

In view of the importance of understanding energy metabolism in cancer and the paucity of data describing TEE in these patients, the objective of this cross-sectional analysis was to characterize TEE by whole-room indirect calorimetry in patients with recently diagnosed stage II-IV colorectal cancer (CRC), investigate predictors of TEE, and compare measured TEE by whole-room indirect calorimetry to predicted energy requirements in cancer (i.e., 25-30 kcal/kg (8)).

Methods

Study Design and Patients

This cross-sectional analysis consists of baseline data from a sample of patients with recently-diagnosed CRC participating in a randomized controlled pilot trial of high-protein diets during anti-cancer therapy (14). The trial was registered at clinicaltrials.gov (NCT02788955) and the trial protocol has been published (15). Clinical assessments were completed at the Human Nutrition Research Unit (16), at the University of Alberta (Edmonton, Canada) prior to patients being randomized and receiving the intervention in the larger trial. A $50 (CAD) grocery store gift card was given to patients who completed this 24-hour whole-room indirect calorimetry assessment. Of the 50 patients who completed baseline assessments for the larger trial, 31 patients completed the optional 24-hour whole-room indirect calorimetry assessment and were included herein. Findings from this convenience sample are presented herein and can be used to design future studies.

Inclusion/exclusion criteria did not differ from the larger trial (15). Briefly, patients were 18-85 years of age, had been diagnosed with stage II-IV CRC within the past 7 months, did not present with cancer cachexia (17), and had started or were scheduled to start chemotherapy within 14 days of completing study assessments. Medications that affect energy metabolism or body composition (e.g., new dose of thyroid disorder medication) were exclusionary. The study was approved by the Health Research Ethics Board of Alberta-Cancer Committee (HREBA.CC-15-0193) and complied with standards on the use of human participants in research. All patients provided written informed consent prior to any study assessments. The Room Indirect Calorimetry Operating and Reporting Standards, version 1.0 guided reporting of this study, where applicable (10).

Patient Characteristics

Demographic and clinical characteristics including patient age, sex, disease and treatment history were obtained from electronic health records. Stage of disease was determined by the patient's medical team using the tumor, node, metastasis staging system (18). A study-specific questionnaire that included race categories (Arab, Black, Chinese, Filipino, Indigenous Peoples, Japanese, Korean, Latin American, South Asian, Southeast Asian, West Asian, White/Caucasian) based on the Canadian census was used to collect data on self-reported race.

Anthropometry and Body Composition Assessments

Prior to entering the whole-room indirect calorimeter, height was measured once to the nearest 0.1 cm using a 235 Heightronic Digital Stadiometer (Quick Medical, Issaquah, Wash., USA). Body weight was measured to the nearest 0.1 kg with patients wearing thin, light clothing. The average of 3 measurements taken on a calibrated digital scale (Health o meter® Professional Remote Display, Sunbeam Products Inc., Boca Raton, Fla., USA) was used. Weight was reassessed immediately following TEE assessment to quantify 24-hour weight change. BMI was calculated and categorized per the Centers for Disease Control (19).

Body composition was assessed by whole-body dual-energy X-ray absorptiometry (DXA; General Electric Lunar iDXA High Speed Digital Fan Beam Densitometer with Encore 13.60 software [General Electric Company, Madison, WI, USA]) within 12 days of 24-hour TEE assessment. Estimates of lean soft tissue (LST), fat mass, and bone mineral content were generated at the whole-body and regional levels. Fat-free mass was calculated by summing LST and bone mineral content values. Appendicular LST (ALST) was calculated by summing LST of the limbs. Both ALST and LST were reported to account for the presence of tumor(s) when whole-body LST was considered (20, 21).

Whole-room Indirect Calorimeter

Energy expenditure was assessed by 24-hour stay in a whole-room indirect calorimeter within 2 weeks of starting chemotherapy and prior to receiving the trial intervention. An open-circuit room calorimeter was used to measure volumes of O_2 and CO_2 exchanged. An air conditioning system ran at 0.193 m^3/s to maintain a temperature range of 21–23°C and relative humidity <70%. The system mixed air within the room at a rate of 0.193 m^3/s; thus, the totality of air within the room circulated through the air conditioner every 2 minutes and 30 seconds. Fresh air was drawn passively from the buffer zone into the room through a fresh air inlet at 60 liters/minute and mixed expired air was withdrawn from the room by a minispiral fan. Extraction of air facilitated by the minispiral fan resulted in a slightly negative constant pressure within the room. A sample gas cooler set to 1°C reduced and help regulate moisture (condensate) in the air before it was pumped at a flow rate of 1 liter/minute into O_2 (Oxymat 6, Siemens AG, Munich, Germany) and CO_2 (Advance Optima AO2000 Series, ABB Automation GmbH, Frankfurt, Germany) differential analyzers to capture gas volumes within the room and buffer zone every 1-minute throughout the assessment period. Calculated difference in O_2 and CO_2 concentrations between the room calorimeter and the buffer zone were transmitted from the gas analyzers to a desktop computer by the National Instruments NI USB-6221 device (National Instruments Corporation, Austin, Texas, USA) and displayed on the screen via Pennington Metabolic Chamber Software Suite version 1.8 (Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA). CO_2 and O_2 analyzers were calibrated once per week by conducting a “zero test” (i.e., recording gas exchange rates of the fresh air in the buffer zone versus itself) and a span gas calibration (i.e., recording gas exchange rates of the span gas bottle versus the buffer zone). The room calorimeter was calibrated prior to each assessment with pre-mixed gas (20% O_2; 1% CO_2; balanced with nitrogen) and a 24-hour propane burn test was conducted quarterly.

The room calorimeter used in this study and its analytical components were previously tested for reliability using a test re-test approach with 1 day between assessments. The coefficient of variation was 2.2% for TEE in n=10 healthy participants (Human Nutrition Research Unit, personal communications).

Total Energy Expenditure Assessment

Patients were advised to refrain from using nicotine the morning of assessments, consuming any calories or caffeine for 10 hours prior, and from physical activity and alcohol consumption for 24 hours prior (12). Water, medication, and minimal activity (e.g., activities of daily living) were allowed. The use of elevators and motor vehicles for transportation to the research unit on the morning of the assessments were encouraged.

The TEE assessment lasted 23 hours and 15 minutes. The software algorithm required 30 minutes of measurements before calculations of energy expenditure began, thus 22 hours and 45 minutes of data were obtained within the assessment period. Data were extrapolated to a 24-hour period: the first 15 minutes of data were duplicated and added to the beginning of the data set and the first 60 minutes of data were duplicated and added to the end of the data set to obtain 24 hours of data. This standard approach has been used for all TEE assessment studies conducted in our room calorimeter (22, 23). Minute-by-minute volume of O_2 consumption and volume of CO_2 production were summed and used to calculate TEE using the Weir equation accounting for urinary nitrogen (24).

The whole-room indirect calorimeter (**Supplementary Figure 1**) had a geometric volume of 28.74 m^3. Patients followed a standardized schedule (**Supplementary Table 1**) and were allowed to sleep, if needed, to ameliorate cancer-related fatigue. Rest time did not alter mealtimes or other activities; the patient was awoken for scheduled activities.

Dietary Intake During the 24-hour Room Calorimeter Assessment

A REE assessment in the calorimetry chamber was conducted up to two weeks prior to the TEE assessment as part of the larger trial (15). Briefly, participants were instructed to avoid caffeine, alcohol, and eating, strenuous movement, and nicotine before REE testing, similar to pre-TEE testing protocols and as previously described in detail (15). REE was multiplied by an assumed activity factor of 1.2 (sedentary activity level) and a coefficient of 1.075 to account for thermic effects of food (25) to estimate energy requirements throughout the assessment period and promote energy balance. A metabolic cart (Vmax® Encore [CareFusion, Yorba Linda, California, USA]) was used to estimate caloric requirements for the 24-test day in cases where the room calorimeter was not available. Regardless of pre-test REE assessment method, adjustments to the caloric content of the diet were made to the closest 100 kcal at three timepoints during the 24-hour room calorimeter assessment (**Supplementary Table 1**) using average energy expenditure per minute data from the ongoing assessment. Adjustments are required to ensure that effects of diet composition and energy intake are removed, and energy expenditure differences and associations are merely a reflection of the phenotypes of interest. Patients were provided a standardized isocaloric diet that consisted of three meals and two snacks; and a low-fiber menu option was available, **Supplementary Table 2**. The macronutrient distribution of both menu options is shown in **Supplementary Table 3** and was approximately 50% carbohydrate, 30% fat, and 20% protein. Food was prepared in a metabolic kitchen and weighed to the nearest 0.1 gram. Water and herbal tea were provided *ad-libitum* and no caffeine was consumed during the 24-hour test. Patients were encouraged to eat all provided food; however, consuming all food was not possible for all participants. Items not consumed were weighed prior to disposal. Dietary intake from the 24-hour assessment period was evaluated using The Food Processor® Nutrition and Fitness Software (version 11.7.217, ESHA Research, Salem, Oregon, USA).

Urine Analysis

Patients voided their bladder prior to entering the room calorimeter and were provided sterile 3 L urine jugs and instructed to collect all voided urine throughout the 24-hour assessment. On day 2, patients voided their bladder prior to exiting the room. Urine collections were kept in a specimen refrigerator throughout the assessment period. Total urine volume was measured, and urine samples (1 mL each) were pipetted into aliquot tubes, frozen, and stored in a -80°C freezer. For analysis, thawed urine samples were diluted with double deionized water by a dilution factor of 101 (0.3 mL of urine, 30 mL of dilutant). Diluted samples were combusted to nitric oxide and nitrogen dioxide, and then reacted with ozone to form nitrogen dioxide in an excited state. A chemiluminescence detector (high-temperature Shimadzu TOC-L CPH Model Total Organic Carbon Analyzer with an ASI-L autosampler and TNM-L unit [Shimadzu Corporation, Suzhuo, Jiangsu, China]) measured resultant photon emission. Total urinary nitrogen content (mg/L) of samples was quantified by calibrating the total organic carbon analyzer with ammonium or nitrate salts (coefficient of variation 1.14%). Total nitrogen excretion for the 24-hour period was derived using the below equation:

Total nitrogen excretion (g) = ((sample nitrogen (mg/L]) * dilution factor) * 24-hour urine volume (L)) / 1000

Predicted Energy Requirements

In line with the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on nutrition in cancer patients, energy requirements were predicted to range between 25 and 30 kcal/kg of body weight per day (8) to mimic clinical practice. Body weight was assessed (as previously described) and multiplied by 25 kcal/kg to determine the lower end of predicted energy requirements. Similarly, body weight was multiplied by 30 kcal/kg to determine the upper end of predicted energy requirements.

Statistical Analysis

Data analyses were conducted using IBM SPSS® Statistics version 28 (International Business Machines Corporation, Armonk, NY, USA) or GraphPad Prism version 9.3.1 for Windows (GraphPad Software, San Diego, California, USA). Data were reported as mean ± standard deviation (SD) or median and inter-quartile range in the case of non-normality, unless otherwise stated. Normality was assessed by Shapiro-Wilk test. Significance for all tests was set at $p<0.05$. Continuous dependent variables were compared by sex, tumor location (colon versus rectum), and presence of obesity (BMI <30 kg/m^2 versus BMI ≥ 30 kg/m^2) using independent samples t-test, Welch's t-test in the case of heterogeneity of variances, or Mann-Whitney U test in the case of non-normality. Dichotomous dependent variables were compared using Chi Square test or Fisher's exact test.

Generalized linear models used an identity link function to form a linear relation between the dependent variable (TEE, kcal/day) and predictors hypothesized to affect TEE (age, weight, BMI, fat-free mass [kg and percent], fat mass [kg and percent], fat mass:fat-free mass, LST, ALST, sex, tumor location, disease stage, presence of an ostomy) in unadjusted models. Predictors that were significant in the univariate models were input into adjusted models. Multicollinearity was assessed by variance inflation factor >10. Predictors with multicollinearity were removed from the adjusted model and those that remained significant were kept in the model. Non-significant predictors were removed from the adjusted model until a maximum of three predictors were kept in an adjusted model. The maximum number of predictors was limited to one for every ten participants, assuming that more predictors may result in inaccurate results. Standard model building methods were used for model selection and the most parsimonious model was chosen for the final model. Two adjusted models were presented to consider ALST and LST due to the presence of tumor for some patients in the latter. Results of unadjusted and adjusted models for TEE were presented as beta coefficient (β), 95% confidence interval (CI), and P-value.

Log-log regression models as described and recommended elsewhere (26-28) were used to account for differences in body size and/or composition when assessing TEE. Briefly, a linear regression analysis was used to determine the slope of the regression line that related log (TEE) with log (LST). LST was raised to the power of the relevant slope to adjust for differences in LST between patients. TEE values were expressed as kcal/kg LST^{slope} and plotted against LST by sex and by BMI (BMI <30 kg/m^2 versus BMI ≥ 30 kg/m^2) to remove effects of body composition on TEE (therefore avoiding the incorrect adjustment of TEE/LST). Interaction terms were examined to determine if differences in slopes existed.

Measured TEE was compared to predicted energy requirements in cancer (25–30 kcal/kg (8)) using a paired-samples t-test. Wilcoxon Signed Rank test was used to compare paired samples in the case of non-normality. Bland-Altman plots were used to assess agreement between measured TEE and predicted energy requirement (25 and 30 kcal/kg) variables and were reported based on Standards for a Bland-Altman Agreement Analysis (29). Error was determined as the difference between predicted minus measured TEE values and was reported with 95% CI to indicate group-level agreement between methods. A one sample t-test was used to compare error against a test value of 0. Individual-level agreement was assessed using limits of agreement (error ± 1.96*SD); 95% CI for the upper and lower limits of agreement were considered individually (30). Proportional error was evaluated as the correlation between the mean of predicted and measured TEE and error to determine if error changed with higher levels of energy expenditure. Error between predicted energy requirements and TEE was related to patient characteristics by Pearson correlation.

Results

Patient Characteristics

A total of 31 patients were included in the study; body composition data were missing for n=1 patient, **Supplementary Figure 2**. Patient characteristics are presented by group and sex in **Table 1**, and by tumor location and presence of obesity in **Supplementary Table 4**. Patients were 56 ± 10 years and group-level BMI was classified as overweight. One patient (3.2%) had a BMI classified as underweight (<18.5 kg/m^2) but was not an outlier for TEE or body composition data. Patients were receiving treatment for stage II-IV CRC and chemotherapy started a median of 9 days (25th, 75th percentile: 5, 13 days) prior to study assessments. Nine patients (29.0%), all with a diagnosis of rectal cancer, received radiotherapy a median of 144 days (25th, 75th percentile: 48, 181 days) prior to study assessments. During the 24-hour assessment period, patients achieved energy intake within 100 kcal of predicted requirements (mean energy balance: 73 ± 142 kcal/day), as planned.

Total Energy Expenditure

Absolute TEE (2074 ± 337 kcal/day) differed by sex (**Table 1**), tumor location, and presence of obesity (**Supplementary Table 4**). Patients with rectal cancer had lower absolute TEE (mean [95% CI] difference: -279 [-485, -73] kcal/day; p=0.010). However, TEE expressed per kg body weight did not differ among individuals grouped by sex or cancer type. No differences in absolute TEE or TEE adjusted for body weight were observed by stage (II/III versus IV) of disease. Patients who presented with obesity had greater absolute TEE (mean [95% CI] difference: 393 [-182, 604] kcal/day; p<0.001) and lower TEE per kg body weight (-3.1 [-5.0, -1.3] kcal/kg; p=0.002) compared with patients without obesity.

Predictors of Energy Expenditure

In unadjusted models, weight, BMI, fat-free mass, fat mass, LST, ALST, sex, tumor location, and presence of an ostomy were predictors of TEE (all p<0.05), **Table 2**. Unadjusted predictors of TEE were input in an adjusted model; weight, BMI, and fat-free mass were removed due to collinearity. Presence of an ostomy was then removed, followed by fat mass due to non-significance and a log likelihood ratio <3.84 between models. In the resulting model (model 1), ALST (p<0.001) and tumor location (p=0.023) independently predicted TEE when adjusted for sex. The model was also run with LST instead of ALST (model 2) and found that LST independently predicted TEE (p<0.0001) when adjusted for sex and tumor location, **Table 3**.

The log-log regression model of TEE and LST produced a slope (β) of 0.693 (95% CI: 0.571, 0.814; p<0.001). TEE/LST$^{0.7}$ was plotted against LST to illustrate TEE among patients by sex (**Figure 1A**) and by presence of obesity (**Figure 1B**) after accounting for LST. Two males who both presented without obesity and ~47kg of LST had measured TEE/LST$^{0.7}$ that differed by 39.05 kcal/kg (i.e., 609 kcal/day). The slope of the regression lines for males and females and patients with and without obesity did not differ between groups.

Total Energy Expenditure versus Predicted Energy Requirements

Group-level difference (i.e., error) between measured TEE and predicted energy requirements (25 and 30 kcal/kg) varied (**Table 4**) and was present for the group, by sex, by site, and by presence of obesity, **Figure 2**. Energy requirements predicted using 25 kcal/kg were most accurate at the group level (i.e., smallest error) and energy requirements predicted by 30 kcal/kg were the least accurate. TEE did not differ from the lower bound of predicted energy requirements for patients with cancer (25 kcal/kg) by sex, or by tumor location. Measured TEE was below predicted requirements using 30 kcal/kg by sex (females: -346 ± 290 kcal/day; p=0.004 and males: -470 ± 336 kcal/day; p<0.001) and by tumor location (colon: -492 ± 320; p<0.001 and rectum: -278 ± 291; p=0.021).Proportional error was observed (i.e., error differed at higher TEE) for predicted energy requirements using 25 kcal/kg (r = -0.587; p<0.001) and 30 kcal/kg (r = -0.751; p<0.001). Error from the upper and lower end of the predicted energy requirements range was positively correlated with weight, BMI, and body composition components, **Table 5**. Greater error was observed for patients with obesity (BMI ≥30 kg/m^2 versus BMI <30 kg/m^2) when energy requirements were predicted using 25 kcal/kg (p=0.010) and 30 kcal/kg (p<0.001). Agreement between measured TEE and predicted energy requirements (25 and 30 kcal/kg) by sex, tumor location, and presence of obesity is illustrated in **Supplementary Figure 3A-F.**

On an individual level, the least accurate method (i.e., the widest limits of agreement) was observed for energy requirements predicted at 30 kcal/kg, **Table 4**. More than half of patients (58.1%; n=18) had measured TEE outside of the predicted energy requirement range (25–30 kcal/kg) and most (n=16, 51.6%) were below 25 kcal/kg. Individual patients with measured TEE outside of 25-30 kcal/kg (i.e., under- or over-predicted) trended towards being older compared to patients with measured TEE within the predicted energy requirement range (59 ± 8 versus 52 ± 11 years; p=0.057); no differences were observed by sex, or tumor location. A range of error between predicted energy requirements (25-30 kcal/kg) and measured TEE was observed across patients, **Figure 3**. When predicted energy requirements were compared with measured TEE, energy requirements were underpredicted by up to 378 kcal/day and overpredicted by up to 1111 kcal/day.

Discussion

This study is the largest and only in over 25 years to objectively assess TEE by room calorimeter in patients with cancer. To our knowledge, our study is the first to evaluate TEE in patients with CRC using this technique and supports accurate assessment of TEE and its determinants by a technique that enforces a controlled sedentary environment. Similar to populations without cancer, body composition was a major determinant of TEE; however in this population of patients with CRC, tumor location was an independent predictor of TEE in an adjusted model. In this controlled, sedentary environment, we showed that over half of patients had measured TEE outside of the predicted energy requirement range for people with cancer. These findings suggest that more than half of patients may benefit from individualized nutrition assessment. Given the nature of the assessment technique applied in this study, patients who are not sedentary are especially likely to benefit from individualized nutrition assessment, including energy expenditure assessment in less confined environments. We showed that the upper bound of predicted energy requirements (30 kcal/kg) can overestimate TEE by 1.44 times when measured in a controlled sedentary environment. Patients with rectal cancer presented with lower TEE by up to ~300 kcal/day compared to patients with colon cancer (no difference in prevalence of metastatic disease by tumor location) although difference in TEE was not observed when body weight was considered (kcal/kg). Observed error between measured TEE and predicted energy requirements was higher for patients with obesity and proportional error was observed for energy requirements predicted by 25 kcal/kg and 30 kcal/kg. Taken together, these findings support the need for measured TEE near time of CRC diagnosis to understand individual energy requirements and provide optimal nutrition support. Patients with CRC should be considered a heterogenous group when determining patients that could benefit most from registered dietitian support.

Patients with stage II–IV CRC are commonly treated with radiotherapy and/or chemotherapy. In contrast to most patients with colon cancer, those with rectal cancer typically undergo neoadjuvant chemoradiotherapy prior to surgery and adjuvant chemotherapy (31). In turn, rectal cancer has been associated with increased risk for weight loss, metabolic derangements, decreased treatment tolerability, malnutrition, and subsequently poorer prognosis (32-34). Nonetheless, patients with colon and rectal cancer are often considered as a homogeneous group (i.e., as patients with CRC (35)). We showed that patients with rectal cancer (all received prior chemoradiotherapy) had lower TEE, weight, BMI, fat mass, and were more likely to have an ostomy compared to patients who were treated for colon cancer. Cancer type independently predicted TEE and suggested that patients with rectal cancer had lower TEE by approximately 140 kcal/day compared to patients with colon cancer when adjusted for sex and muscle mass (ALST); the difference in absolute TEE was greater (~300 kcal/day lower in patients with rectal cancer). When error between measured TEE and predicted energy requirements was considered, no difference between tumor site was observed. Nonetheless, it is possible that patients with rectal cancer may benefit from energy expenditure and nutritional assessment including measurement of body composition, given that tumor location was an independent predictor of TEE. It is also possible that our findings related to TEE and rectal cancer were due to the greater use of cytotoxic therapy, prolonged duration with the tumor *in-situ* (due to neoadjuvant treatment), and need for invasive surgery (e.g., tumor resection and/or placement of an ostomy) in patients with rectal cancer (36). Our findings showed that presence of an ostomy resulted in lower TEE compared to patients without an ostomy. Oncology patients with ostomies have been found to have low levels of physical activity (37) which can contribute to decreased TEE.

Our findings suggested that in a highly controlled sedentary environment, TEE was accurately predicted by the lower bound of recommended energy intake in cancer (25 kcal/kg). The upper end of the recommended intake (30 kcal/kg) did not predict TEE for the group. Proportional error was detected for weight-based equations (25-30 kcal/kg) whereby error became increasingly negative (i.e., predicted TEE was progressively different from measured TEE) at higher TEE levels suggesting that the difference between measured and predicted TEE was greater in patients with higher body weight. Weight-based recommendations (i.e., 25-30 kcal/kg) are known to overestimate TEE in patients with obesity (8), likely due to the increased level of adiposity and variable LST (38). This is an important consideration when interpreting our findings as 38.7% of patients presented with obesity. These findings may be in-part explained by the variability in LST and TEE observed in the general population and that the volume of muscle mass is exceeded by adipose tissue beyond a BMI of ~35 kg/m^2 in males and 25 kg/m^2 in females (38).

Body composition and TEE are interrelated and highly dissimilar among individuals (38). Fat free mass, which includes LST, is an established determinant of REE (39) and the impact of cancer-induced changes to body composition on energy expenditure have been explored (26, 40-42). Changes to body composition can alter energy expenditure. Although it has been rarely explored in oncology TEE studies (43), it is important (and recommended) to account for varying body composition phenotypes when assessing and interpreting energy expenditure; as explained in detail by others, this should not be done by using a simple ratio (26-28). Thus, to account for varying body composition profiles, we employed log-log regression models to assess TEE without the effect of body composition. We showed that TEE ranged among patients with CRC who had similar quantities of LST. For example, two males who both presented without obesity and ~47kg of LST had measured TEE/LST$^{0.7}$ that differed by 39.05 (i.e., 609 kcal/day).

TEE guides energy intake recommendations but can be impractical to assess in clinical settings and resource-intensive for research settings. Current oncology nutrition guidelines acknowledge a paucity of evidence on TEE in patients with cancer (8). In practice, energy requirements of patients with cancer are considered similar to those of healthy adults and are estimated using a factor of 25–30 kcal/kg when TEE assessment is not possible (8). These recommendations were guided by studies of patients with severe weight loss (e.g., cancer cachexia) (6), high inflammatory status (7), or early-stage CRC (5). Results from these previous studies suggested that TEE differs among cancer types and stages (5-7, 43, 44). Within our cohort, TEE did not differ between patients with recently diagnosed metastatic disease (stage IV) and those with local or locally-advanced disease (stage II or III). Notably, we screened for severe weight loss, life expectancy, and inflammatory status, and patients with cancer cachexia or acute inflammation were not included (17). With regards to BMI status, we observed similar findings to previous studies whereby individuals with obesity had greater absolute TEE but lower TEE adjusted for body weight, compared to people without obesity (27, 45, 46). While a paucity of studies has assessed TEE in patients with cancer, our laboratory previously published a study of 21 patients with mostly (n=20) stage II-III CRC and found that TEE assessed by doubly-labeled water was 29.7±6.3 kcal/kg (5). These findings were approximately 5.8 kcal/kg higher than results presented herein and could be in part attributed to the sedentary nature of the whole-room calorimeter assessment. Compared to TEE assessed by whole-room indirect calorimetry, doubly-labeled water captures a representative valuation of activity energy expenditure in free-living conditions although variables such as energy intake are much less controlled (47). To our knowledge, no study has assessed free-living TEE in patients with cancer compared with TEE assessed by whole-room indirect calorimetry to quantify observed difference in activity energy expenditure. Overall, findings discussed herein presented a unique approach to TEE assessment in patients with CRC and reflect the precision and accuracy of a whole-room indirect calorimeter for assessment of TEE in a highly controlled sedentary environment (48).

Study limitations: As mentioned, weight-based recommendations (i.e., 25-30 kcal/kg) are routinely used in clinical practice but are known to overestimate TEE in patients with obesity. Additionally, energy expenditure from exercise or physical activity was not captured during the 24-hour assessment to minimize patient burden. Future trials should incorporate use of heart rate sensors or accelerometers to quantify activity (10) as the enforced sedentary environment of room calorimeters can underestimate TEE compared to free-living conditions, particularly for individuals who regularly engage in physical activities not captured by the room calorimeter. Nonetheless, the whole-room indirect calorimeter is highly accurate and measured energy expenditure representative of a structured sedentary day (48). Despite being the largest study to date to assess TEE using accurate techniques in patients with cancer, 31 patients were included which precludes generalization and highlights the need for further investigations in larger groups of patients with different cancer types and treatment.

In conclusion, this study used a classic approach to assess TEE but the application to patients with cancer was novel. Our findings support the need for improved predicted energy requirements in patients with recently diagnosed CRC to optimize nutritional support. We showed that TEE was not uniformly high or low in patients with CRC and was predicted by body composition and tumor location. This suggests that a one-size-fits-all weight-based approach to predicted energy requirements is not appropriate for all patients and should be considered in nutritional guidelines. While the lower bounds of predicted energy requirements may accurately predict TEE in sedentary individuals, TEE fell outside of current recommendations for most patients and proportional error was observed for predicted energy requirements, suggesting that error was greater for patients with higher body weight. Future investigations of TEE predictors in both confined and free-living settings are warranted to better understand predicted energy requirements and if patients experience dynamic changes in energy expenditure throughout cancer treatment.

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Author's Contributions

CMP, NED, MS, MBS, SG, SAP, CP, KLF designed the research; KLF, CFT, and IRD conducted the research; KLF and SG analyzed the data; KLF wrote the first version of the paper;

CMP had primary responsibility for final content and project overall supervision. All authors read and approved the final manuscript.

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Table 1 Characteristics of 31 patients with recently diagnosed colorectal cancer.

Characteristic	Total (n=31)	Males (n=21)	Females (n=10)	P value
Age, years	56 ± 10	57 ± 9	53 ± 10	0.272
Race[1], n (%)				0.348
Filipino	2 (6.5)	2 (9.5)	0 (0.0)	
Indigenous Peoples	4 (12.9)	1 (4.8)	3 (30.0)	
Latin American	2 (6.5)	2 (9.5)	0 (0.0)	
South Asian	1 (3.2)	1 (4.8)	0 (0.0)	
White/Caucasian	22 (71.0)	15 (71.4)	7 (70.0)	
Tumor[1], n (%)				0.260
Colon	22 (71.0)	14 (66.7)	8 (80.0)	
Rectum	9 (29.0)	7 (33.3)	2 (20.0)	
Disease stage[1,2], n (%)				0.310
II/III	23 (74.2)	15 (71.4)	8 (80.0)	
IV	8 (25.8)	6 (28.6)	2 (20.0)	
Chemotherapy[1], n (%)				0.968
Capecitabine	4 (12.9)	3 (14.3)	1 (10.0)	
CAPOX	11 (35.5)	8 (38.1)	3 (30.0)	
FOLFOX	10 (32.3)	6 (28.6)	4 (40.0)	
FOLFIRI	3 (9.7)	2 (9.5)	1 (10.0)	
FOLFIRI + BEVA	3 (9.7)	2 (9.5)	1 (10.0)	
Prior radiotherapy[1], n (%)				0.315
Yes	9 (29.0)	7 (33.3)	3 (30.0)	
No	22 (71.0)	14 (66.7)	7 (70.0)	
Ostomy[1], n (%)				0.288
Yes	11 (35.5)	8 (38.1)	3 (30.0)	
No	20 (64.5)	13 (61.9)	7 (70.0)	
Body weight, kg	83.5 ± 19.0	87.6 (75.3, 103.8)	79.0 (58.0, 81.9)	**0.016**

24-hour weight change, kg	-0.23 ± 0.70	-0.11 ± 0.70	-0.47 ± 0.67	0.184
BMI, kg/m^2	27.9 ± 5.5	28.5 ± 5.6	26.6 ± 5.4	0.386
TEE, kcal/day	2074 ± 337	2201 ± 328	1809 ± 152	**<0.001**[†]
TEE, kcal/kg	23.9 (23.2, 28.7)	25.2 ± 3.1	25.7 ± 3.5	0.706
Energy intake, kcal/day	2148 ± 338	2286 ± 314	1857 ± 149	**<0.001**[†]
Energy balance, kcal/day	73 ± 142	86 ± 142	47 ± 147	0.491
Fat mass[3], kg	28.8 ± 11.1	30.5 (19.9, 36.0)	34.2 (16.9, 36.6)	0.880
Fat mass[3], %	34.0 ± 8.8	31.8 ± 8.1	38.3 ± 8.8	0.052
Fat-free mass[3], kg	53.7 ± 11.2	59.0 ± 10.0	43.2 ± 3.1	**<0.001**[†]
Fat-free mass[3], %	66.0 ± 8.8	68.2 ± 8.1	61.7 ± 8.8	0.052
FM:FFM[3]	0.54 ± 0.20	0.48 ± 0.16	0.65 ± 0.22	**0.027**
ALST[3], kg	23.0 ± 5.9	25.6 ± 5.3	17.7 ± 1.8	**<0.001**[†]
LST, kg[3]	50.9 ± 10.7	55.9 ± 9.6	40.8 ± 3.0	**<0.001**[†]

Data presented as mean ± standard deviation or median (25th, 75th percentiles) for non-normally distributed variables. Differences assessed using independent samples t-test or Mann-Whitney U test in the case of non-normal distribution of one or more groups. [†]Welch t-test used due to heterogeneity of variances. Bolded values are significant at $p<0.05$. [1]Fisher's exact test applied (Chi square test assumption violated [expected <5]). [2]Stage of disease grouped as per tumor, node, metastasis staging (18). Briefly, stage II: disease is localized to primary tumor site; Stage III: disease involves the lymph node(s); Stage IV: disease has spread to distant organ(s). [3]n=30; 1 patient missing body composition data. ALST: appendicular lean soft tissue; CAPOX: drug combination of capecitabine and oxaliplatin; FFM: fat-free mass; FM: fat mass; FOLFIRI: drug combination of leucovorin calcium, fluorouracil, and irinotecan hydrochloride; FOLFIRI + BEVA: drug combination of leucovorin calcium, fluorouracil, and irinotecan hydrochloride plus bevacizumab; FOLFOX: drug combination of leucovorin calcium, fluorouracil, and oxaliplatin; kcal: kilocalories; LST: lean soft tissue; TEE: total energy expenditure.

Table 2: Parameter estimates for unadjusted predictors of total energy expenditure in 31 patients with colorectal cancer.

	TEE, kcal/day		
Variables	***β***	**95% CI**	**P value**
Age, years	8.90	-2.86, 20.66	0.138
Weight, kg	15.44	12.41, 18.47	**<0.0001**
BMI, kg/m^2	43.57	28.61, 58.54	**<0.001**
FFM[1], kg	27.05	22.75, 31.34	**<0.0001**
FFM[1], %	-5.23	-18.70, 8.23	0.446
FM[1], kg	16.96	8.14, 25.78	**<0.001**
FM[1], %	5.23	-8.23, 18.70	0.446
FM:FFM[1]	149.48	-454.01, 752.96	0.627
LST[1], kg	28.37	23.85, 32.89	**<0.0001**
ALST[1], kg	50.47	41.14, 59.81	**<0.0001**
Sex			
Female	0		
Male	391.20	183.22, 599.18	**<0.001**
Tumor location			
Rectum	0		
Colon	278.53	41.10, 515.97	**0.021**
Disease stage			
II/III	0		
IV	76.66	-188.45, 341.77	0.571
Ostomy			
No	0		
Yes	-283.68	-505.98, -61.37	**0.012**

Generalized linear models used an identity link function to form a linear relation between the dependent variable (TEE, kcal/day) and predictors hypothesized to affect TEE (age, weight, BMI, fat-free mass [kg and percent], fat mass [kg and percent], fat mass:fat-free mass, LST, ALST, sex, tumor location, disease stage, presence of an ostomy). Bolded values are significant at $p<0.05$. [1]n=30; 1 patient missing dual-energy X-ray absorptiometry-derived data. 95% CI: 95% confidence interval; ALST: appendicular lean soft tissue; *β*: regression coefficient; FFM: fat-free mass; FM: fat mass; kcal: kilocalories; LST: lean soft tissue; SE: standard error; TEE: total energy expenditure.

Table 3: Parameter estimates for adjusted predictors of total energy expenditure in 30 patients with colorectal cancer

Variables	***β***	**95% CI**	**P value**
TEE			
Model 1			
ALST, kg	46.72	34.27, 59.17	**<0.001**
Sex			
Female	0		
Male	25.59	-124.79, 175.96	0.739
Tumor location			
Rectum	0		
Colon	139.69	19.44, 259.95	**0.023**
Model 2			
LST, kg	28.42	22.03, 34.80	**<0.0001**
Sex			
Female	0		
Male	-36.17	-176.42, 104.08	0.613
Tumor location			
Rectum	0		
Colon	99.44	-10.56, 209.44	0.076

Predictors that were significant in the univariate generalized linear models were input into adjusted models. Multicollinearity was assessed by variance inflation factor >10. Predictors with multicollinearity were removed from the adjusted model and those that remained significant were kept in the model. Non-significant predictors were removed from the adjusted model until a maximum of three predictors were kept in an adjusted model. The maximum number of predictors was limited to one for every ten participants, assuming that more predictors may result in inaccurate results. Standard model building methods were used for model selection and the most parsimonious model was chosen for the final model. Two adjusted models were presented to consider ALST and LST due to the presence of tumor for some patients in the latter. Bolded values are significant at $p<0.05$. 95% CI: 95% confidence interval; ALST: appendicular lean soft tissue; β: regression coefficient; LST: lean soft tissue; SE: standard error; TEE: total energy expenditure. In model 1 and 2, TEE was the dependent variable and ALST and LST, respectively, were entered as predictors. All models included sex and tumor location as predictors.

Table 4. Agreement between measured total energy expenditure and predicted energy requirements for 31 patients with colorectal cancer[1].

	kcal/day[2]	Error (95% CI)	Absolute LOA	Lower LOA (95% CI)	Upper LOA (95% CI)
Measured TEE	2074 ± 337				
25 kcal/kg	2087 ± 476	-13 (-103, 77)	961	-493 (-684, -37)	468 (344, 659)
30 kcal/kg	2505 ± 571	-430 (-548, -312)	1263	-1062 (-1313, -900)	201 (39, 452)

Error was determined as the difference between predicted minus measured TEE values and was reported with 95% CI to indicate group-level agreement between methods. Individual-level agreement was assessed using limits of agreement (error ± 1.96*SD); 95% CI for the upper and lower limits of agreement were considered individually. [1]Values are reported in kcal/day. [2]Values are mean ± standard deviation. LOA: limits of agreement; TEE: total energy expenditure.

Table 5. Correlation of absolute error between measured TEE and predicted energy requirements (kcal/day) with characteristics of 31 patients with colorectal cancer.

	Age	**Weight**	**BMI**	**FM[1]**	**FFM[1]**	**FM:FFM[1]**	**LST[1]**	**ALST[1]**	**ALSTI[1]**
25 kcal/kg	0.246	0.743***	0.767***	0.874***	0.391*	0.721***	0.393*	0.454*	0.502**
30 kcal/kg	0.278	0.861***	0.850***	0.920***	0.547**	0.680***	0.549**	0.600***	0.641***

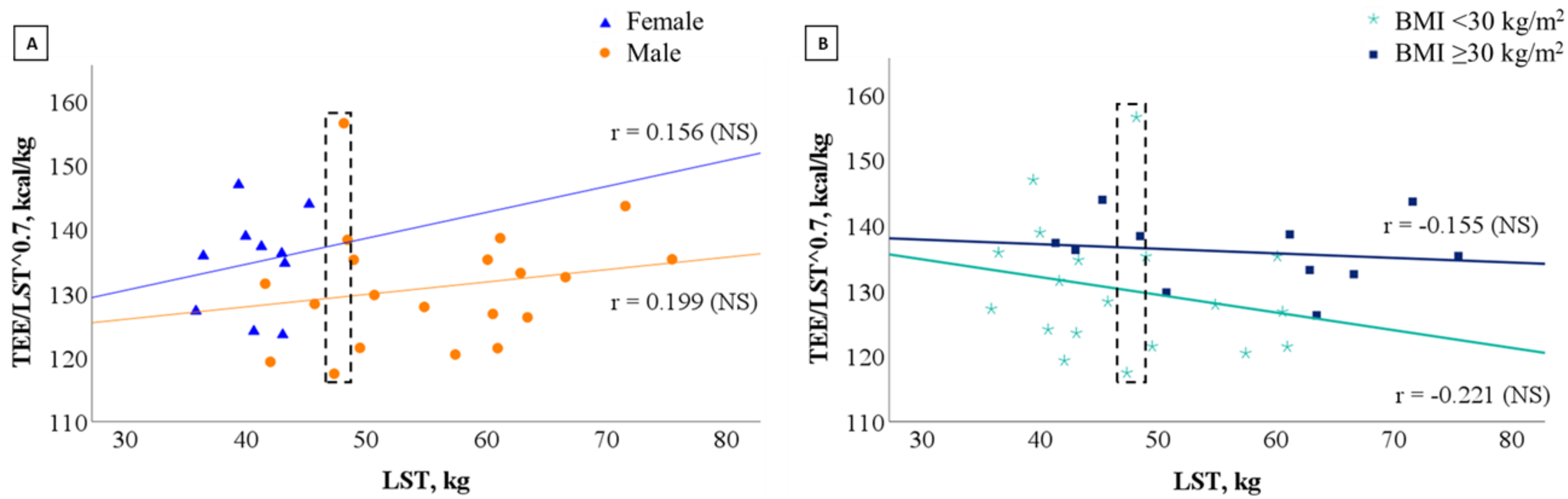
Absolute error calculated as predicted energy requirements minus TEE. 1n=30. *p<0.05; **p<0.01; ***p<0.001 for Pearson correlation. ALST: appendicular lean soft tissue; ALSTI: appendicular lean soft tissue index; BMI: body mass index; FFM: fat-free mass; FM: fat mass; LST: lean soft tissue; TEE: total energy expenditure.

Figure Titles and Legends

Figure 1 A-B. Relationship between total energy expenditure adjusted per kilogram of lean soft tissue raised to the power of 0.7 and lean soft tissue by sex (A) and by presence of obesity (B). As an example, these figures highlight in the hashed boxes that two males who both presented without obesity and ~47kg of LST had measured TEE/LST$^{0.7}$ that differed by 39.05, which is equivalent to measured total energy expenditure that differed by 609 kcal/day. kcal: kilocalorie; LST: lean soft tissue; NS: non-significance; TEE: total energy expenditure. N=30 patients with colorectal cancer (n=10 females; n=20 males; n=19 BMI <30 kg/m^2; n=11 BMI ≥30 kg/m^2).

Figure 2. Absolute error between measured TEE and predicted energy requirements in kcal/day in 31 patients with colorectal cancer. Error calculated as predicted energy requirements minus TEE. Data are mean and 95% confidence interval. *p<0.05 for one sample t-test; test value: 0. n=10 females; n=21 males. n=22 colon cancer; n=9 rectal cancer. n=19 BMI<30 kg/m^2; n=12 BMI ≥30 kg/m^2.

Figure 3. Measured and predicted energy expenditure of 31 patients with colorectal cancer. Each vertical series of triplicate points represents one patient. Hashed box highlights that recommended intake of 25 kcal/kg underestimated energy requirements by up to 378 kcal/day. Dotted box highlights that recommended intake of 30 kcal/kg overestimated energy requirements by up to 1111 kcal/day. kcal: kilocalories; TEE: total energy expenditure.



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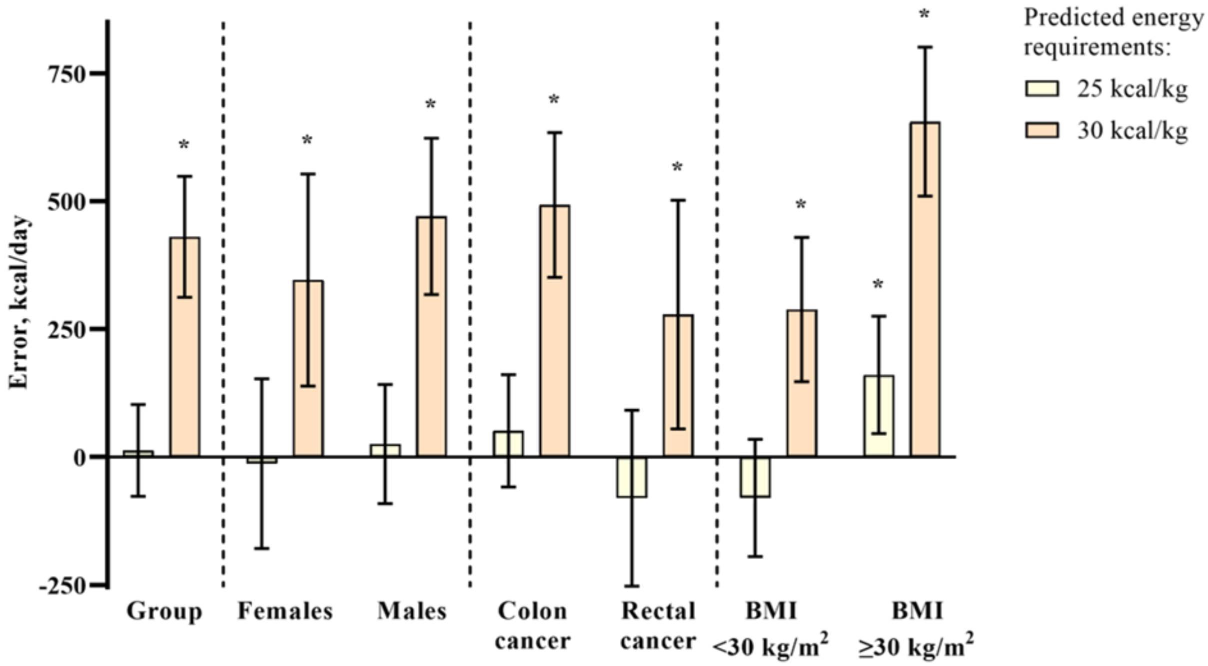

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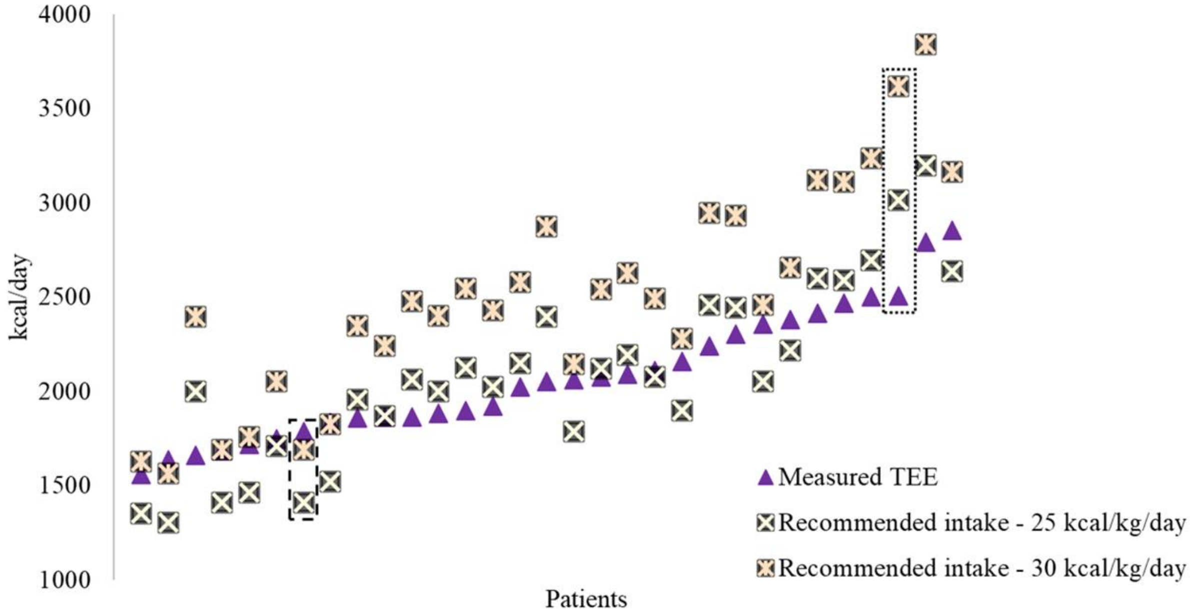

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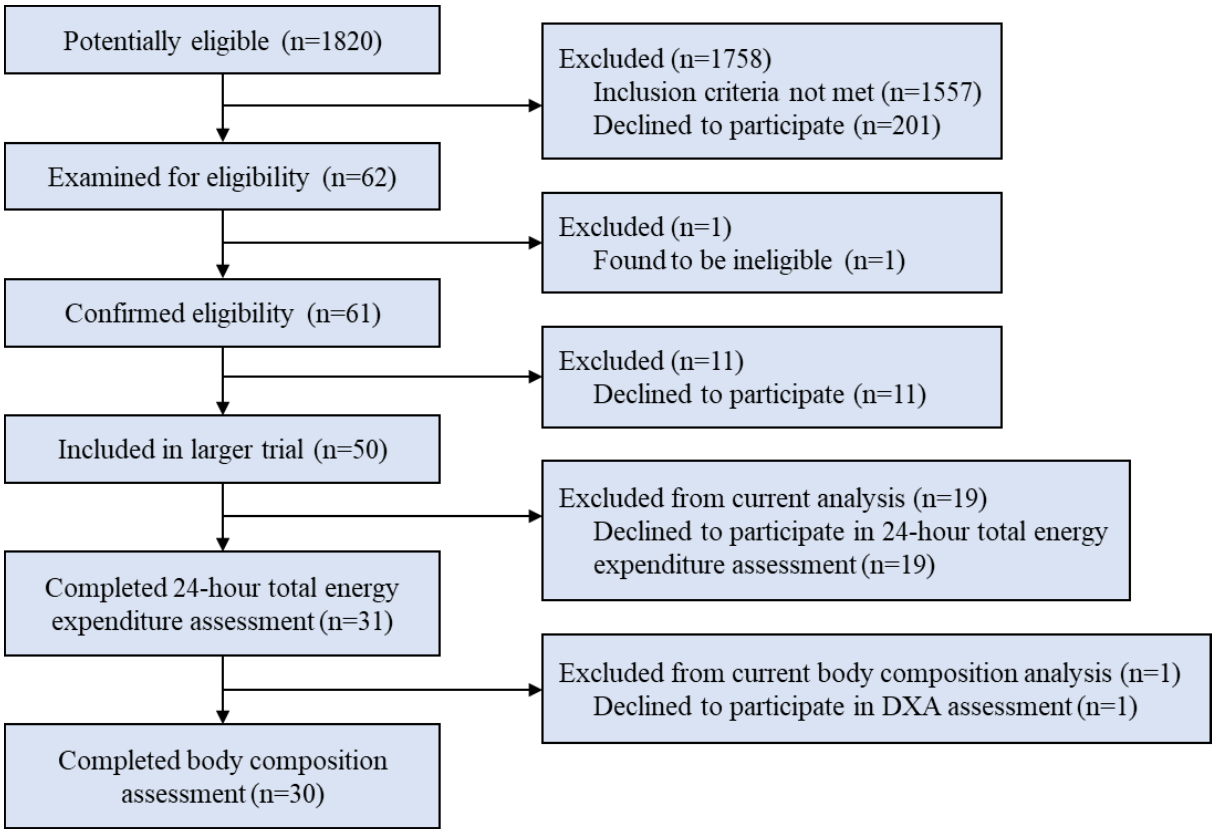
Total energy expenditure assessed by 24-hour whole-room indirect calorimeter in patients with colorectal cancer: baseline findings from the PRIMe study
Ford et al.
Online Supplementary Material

Supplementary Figure 1. View inside of the whole-room indirect calorimeter located within the Human Nutrition Research Unit at the University of Alberta. For a virtual tour please go to: https://app.lapentor.com/sphere/hnru-tour. Photo courtesy of the Human Nutrition Research Unit, University of Alberta.

Total energy expenditure assessed by 24-hour whole-room indirect calorimeter in patients with colorectal cancer: baseline findings from the PRIMe study
Ford et al.
Online Supplementary Material

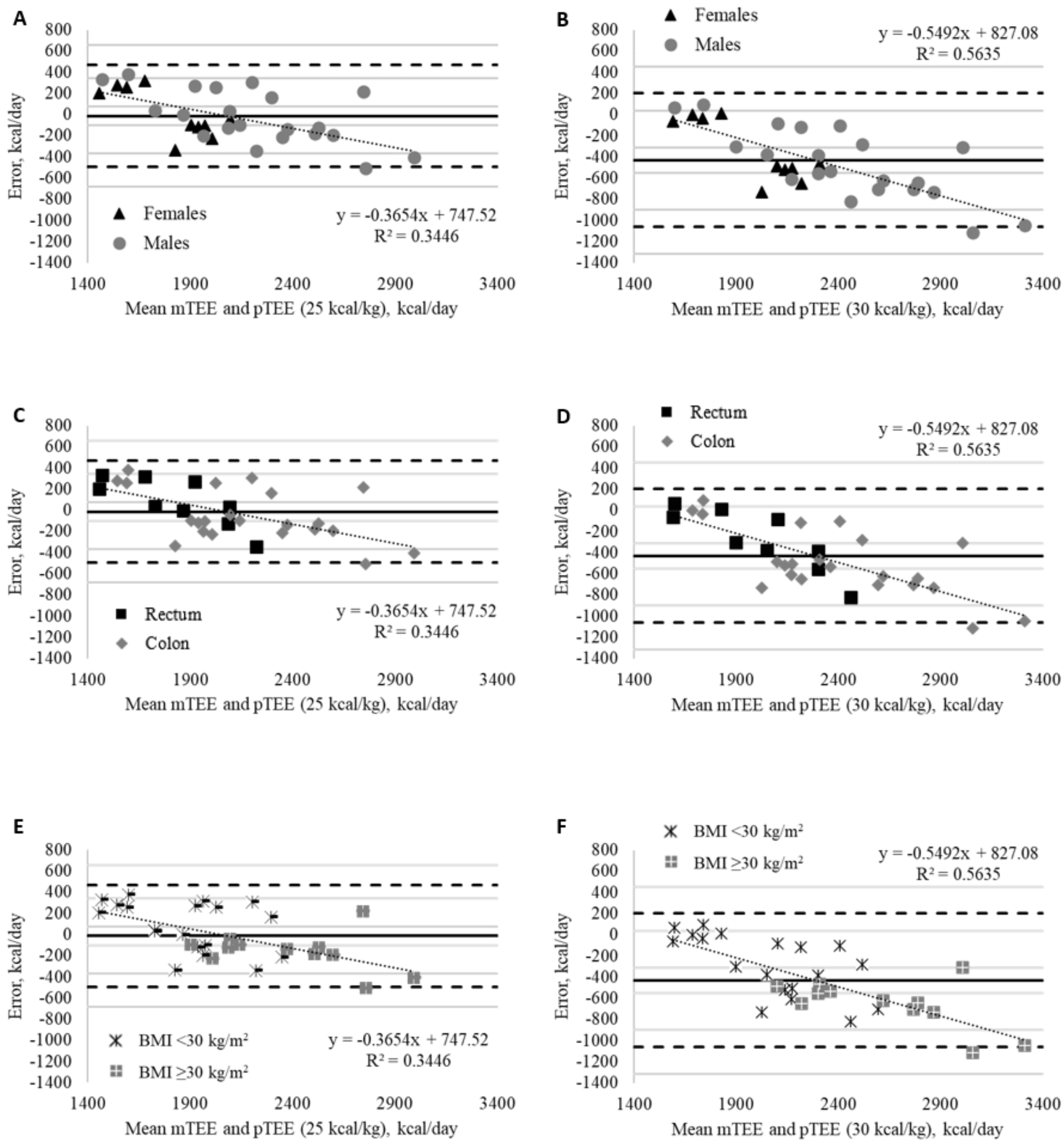


Supplementary Figure 2. Flow diagram of patients with colorectal cancer recruited as part of a larger ongoing trial. This manuscript presents a secondary cross-sectional analysis of baseline data from a convenience sample of patients with newly diagnosed colorectal cancer participating in a larger trial. The 24-hour total energy expenditure assessment by whole-room indirect calorimetry was an optional component of the larger trial offered to all participants who completed baseline assessments. DXA: dual-energy X-ray absorptiometry.

Total energy expenditure assessed by 24-hour whole-room indirect calorimeter in patients with colorectal cancer: baseline findings from the PRIMe study

Ford et al.

Online Supplementary Material



Supplementary Figure 3 A-F. Bland-Altman plots of total energy expenditure measured by indirect calorimetry and total energy expenditure predicted by the lower bound of predicted energy requirements in cancer (25 kcal/kg) by sex (A), tumor location (C), and presence of obesity (E); the upper bound of predicted energy requirements in cancer (30 kcal/kg) by sex (B), tumor location (D), and presence of obesity (F) in 31 patients with colorectal cancer. Solid black line represents the mean error; hashed lines represent the 95% limits of agreement (error ± 1.96 x standard deviation); solid grey lines represent the 95% confidence intervals for the error and limits of agreement. Black triangles represent female patients; grey circles represent male patients (A-B); black squares represent patients with rectal cancer; grey triangles represent patients with colon cancer (C-D); black star represents patients with a BMI <30 kg/m^2; grey cubes represent patients with a BMI ≥30 kg/m^2. The difference between measured and predicted TEE was expressed as absolute kcal per day. kcal: kilocarlorie; mTEE: measured total energy expenditure; pTEE: predicted total energy expenditure; kcal/kg: kcal per kg body weight per day.

Total energy expenditure assessed by 24-hour whole-room indirect calorimeter in patients with colorectal cancer: baseline findings from the PRIMe study
Ford et al.
Online Supplementary Material

Supplementary Table 1. Patient Schedule in the Whole-room Indirect Calorimeter

Time	Task
Day 1	
8:00 a.m.	24-hour energy expenditure assessment begins
8:45 a.m.	Energy expenditure prediction using calorimeter data
9:00 – 9:30 a.m.	Morning meal (asked to consume all food within thirty minutes)
9:30 a.m. – 12:00 p.m.	Leisure time (e.g., computer, television, reading)
11:15 a.m.	Energy expenditure prediction using calorimeter data
12:00 – 12:30 p.m.	Mid-day meal (asked to consume all food within thirty minutes)
12:30 – 2:30 p.m.	Leisure time (e.g., computer, television, reading)[1]
2:30 – 3:00 p.m.	Afternoon snack (asked to consume all food within thirty minutes)
3:00 – 5:00 p.m.	Leisure time (e.g., computer, television, reading)
3:15 p.m.	Energy expenditure prediction using calorimeter data
5:00 – 5:30 p.m.	Evening meal (asked to consume all food within thirty minutes)
5:30 – 8:00 p.m.	Leisure time (e.g., computer, television, reading)
8:00 – 8:30 p.m.	Evening snack (asked to consume all food within thirty minutes)
8:30 – 10:00 p.m.	Leisure time
10:00 p.m.	Sleep
Day 2	
6:00 a.m.	Wake-up call and reminder to void bladder
7:15 a.m.	Exit the whole-room indirect calorimeter

[1]A subset of patients completed a semi-structured interview over the phone during the 24-hour assessment. Results from that study are published elsewhere (49).

Supplementary Table 2. Sample of regular and low-fiber menu items provided to patients during the 24-hour whole-room indirect calorimeter assessment

	Regular Menu	**Low-fiber Menu**
Morning meal	Eggs, scrambled Toast, whole wheat Peanut butter Juice, orange	Eggs, scrambled Toast, white Margarine Juice, apple
Mid-day meal	Turkey wrap • Tortilla, flour • Turkey, deli • Dressing, ranch • Cheese, cheddar • Lettuce, romaine • Tomato, diced Tomato soup Peaches, canned in juice[1] Yogurt, vanilla[1]	Turkey wrap • Tortilla, flour • Turkey, deli • Dressing, ranch • Cheese, cheddar Tomato soup Peaches, canned in juice[1] Yogurt, vanilla[1]
Afternoon snack	Apple Crackers, multigrain Cheese, mozzarella Yogurt, vanilla[1]	Applesauce Crackers, multigrain Cheese, mozzarella Yogurt, vanilla[1]
Evening meal	Chicken stir fry • Chicken breast • Celery • Carrot • Onion • Soy sauce • Ginger • Garlic Rice, brown Yogurt, vanilla[1]	Chicken stir fry • Chicken breast • Soy sauce • Ginger • Garlic Rice, white Yogurt, vanilla[1]
Evening snack	Almonds Milk[1] Cereal, Cheerios[1] Peaches, canned in juice[1]	Bread, white Margarine Jam, seedless Milk Peaches, canned in juice[1]

[1]use of these menu items varied depending on the caloric needs of the patient.

Supplementary Table 3. Macronutrient composition of a 2000 kilocalorie regular and low-fiber study diet

	Target	**Regular Menu**	**Low-fiber Menu**
Energy, kcal	2000	2020	1998
Carbohydrate			
Grams	250	247	258
% of energy	50	49	52
Fat			
Grams	67	66	62
% of energy	30	29	28
Protein			
Grams	100	111	101
% of energy	20	22	20

kcal: kilocalories.

Supplementary Table 4. Characteristics of 31 patients with recently diagnosed colorectal cancer by tumor location and presence of obesity.

	Tumor Location			Presence of Obesity		
Characteristic	**Rectum (n=9)**	**Colon (n=22)**	**P value**	**BMI <30 kg/m^2 (n=19)**	**BMI ≥30 kg/m^2 (n=12)**	**P value**
Age, years	53 (47, 58)	60 (54, 63)	0.064	54 ± 10	59 ± 8	0.160
Sex[1], n (%)			0.259			0.250
Male	7 (77.8)	14 (63.6)		12 (63.2)	9 (75.0)	
Female	2 (22.2)	8 (36.4)		7 (36.8)	3 (25.0)	
Race[1], n (%)			0.801			0.610
Filipino	1 (11.1)	1 (4.5)		2 (10.5)	0 (0.0)	
Indigenous Peoples	1 (11.1)	3 (13.6)		2 (10.5)	2 (16.7)	
Latin American	1 (11.1)	1 (4.5)		2 (10.5)	0 (0.0)	
South Asian	0 (0.0)	1 (4.5)		1 (5.3)	0 (0.0)	
White/Caucasian	6 (66.7)	16 (72.7)		12 (63.2)	10 (83.3)	
Tumor[1], n (%)						**0.045**
Colon				11 (57.9)	11 (91.7)	
Rectum				8 (42.1)	1 (8.3)	
Disease stage[1,2], n (%)			0.280			0.324
II/III	6 (66.7)	17 (77.3)		14 (73.7)	9 (75.0)	
IV	3 (33.3)	5 (22.7)		5 (26.3)	3 (25.0)	
Chemotherapy[1], n (%)			0.091			0.313
Capecitabine	3 (33.3)	1 (4.5)		4 (21.1)	0 (0.0)	
CAPOX	2 (22.2)	9 (40.9)		5 (26.3)	6 (50.0)	
FOLFOX	2 (22.2)	8 (36.4)		7 (36.8)	3 (25.0)	

FOLFIRI	2 (22.2)	1 (4.5)		2 (10.5)	1 (8.3)	
FOLFIRI + BEVA	0 (0.0)	3 (13.6)		1 (5.3)	2 (16.7)	
Prior radiotherapy[1], n (%)			**<0.001**			**0.045**
Yes	9 (100.0)	0 (0.0)		8 (42.1)	1 (8.3)	
No	0 (0.0)	22 (100.0)		11 (57.9)	11 (91.7)	
Ostomy[1], n (%)			**<0.001**			**0.013**
Yes	8 (88.9)	3 (13.6)		10 (52.6)	1 (8.3)	
No	1 (11.1)	19 (86.4)		9 (47.4)	11 (91.7)	
Body weight, kg	71.8 ± 14.7	88.2 ± 18.8	**0.027**	73.7 ± 14.1	99.0 ± 15.3	**<0.001**
24-hour weight change, kg	-0.14 ± 0.37	-0.26 ± 0.80	0.677	-0.33 ± 0.49	-0.06 ± 0.94	0.373†
BMI, kg/m^2	23.9 ± 4.2	29.5 ± 5.2	**0.008**	24.5 ± 3.8	33.3 ± 2.8	**<0.001**
TEE, kcal/day	1877 ± 200	2155 ± 351	**0.010**†	1922 ± 244	2315 ± 330	**<0.001**
TEE, kcal/kg	25.6 (24.3, 29.5)	23.7 (22.8, 27.4)	0.113	26.6 ± 3.4	23.5 ± 1.5	**0.002**†
Energy intake, kcal/day	2032 ± 225	2195 ± 369	0.227	2018 ± 234	2354 ± 383	**0.015**†
Energy balance, kcal/day	155 ± 144	40 ± 131	**0.039**	96 ± 135	38 ± 153	0.284
Fat mass[3], kg	22.0 ± 8.9	31.7 ± 10.9	**0.025**	24.0 (16.5, 33.4)	36.2 (32.4, 38.8)	**<0.001**
Fat mass[3], %	29.7 ± 7.6	35.8 ± 8.7	0.076	31.1 ± 9.3	38.9 ± 5.1	**0.016**
Fat-free mass[3], kg	49.9 (43.6, 55.9)	51.2 (44.7, 65.3)	0.326	49.9 ± 8.6	60.4 ± 12.6	**0.026**†
Fat-free mass[3], %	70.3 ± 7.6	64.2 ± 8.7	0.076	68.9 ± 9.3	61.1 ± 5.1	**0.016**
FM:FFM[3]	0.44 ± 0.14	0.58 ± 0.20	0.055	0.48 ± 0.20	0.65 ± 0.13	**0.021**
ALST[3], kg	21.1 ± 3.7	23.8 ± 6.5	0.161†	20.9 ± 4.3	26.6 ± 6.6	**0.021**†
LST, kg[3]	47.0 ± 7.0	52.5 ± 11.7	0.123†	47.2 ± 8.2	57.2 ± 11.9	**0.025**†

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Ford et al.

Online Supplementary Material

Data presented as mean ± standard deviation or median (25^{th}, 75^{th} percentiles) for non-normally distributed variables. Differences assessed using independent samples t-test or Mann-Whitney U test in the case of non-normal distribution of one or more groups. [†]Welch t-test used due to heterogeneity of variances. Bolded values are significant at $p<0.05$. [1]Fisher's exact test applied (Chi square test assumption violated [expected <5]). [2]Stage of disease grouped as per tumor, node, metastasis staging (18). Briefly, stage II: disease is localized to primary tumor site; Stage III: disease involves the lymph node(s); Stage IV: disease has spread to distant organ(s). [3]n=30; 1 patient missing body composition data. ALST: appendicular lean soft tissue; CAPOX: drug combination of capecitabine and oxaliplatin; FFM: fat-free mass; FM: fat mass; FOLFIRI: drug combination of leucovorin calcium, fluorouracil, and irinotecan hydrochloride; FOLFIRI + BEVA: drug combination of leucovorin calcium, fluorouracil, and irinotecan hydrochloride plus bevacizumab; FOLFOX: drug combination of leucovorin calcium, fluorouracil, and oxaliplatin; kcal: kilocalories; LST: lean soft tissue; TEE: total energy expenditure.