ORIGINAL

Association of energy expenditure with body composition and nutritional intake in male patients with esophageal and head and neck cancer

Ayako Tatsumi[1,2*], Momoko Kyomen[1,2*], Rie Tsutsumi[1,3], Kana Beppu[1], Rina Aihara-Matsushima[1], Yuna Izumi-Mishima[1], Sonoko Yasui-Yamada[1], Yasuo M. Tsutsumi[3], Kazuhiro Nomura[1,4], and Hiroshi Sakaue[1,4]

[1]Department of Nutrition and Metabolism, Institute of Biomedical Science, Tokushima University Graduate School, Tokushima, [2]Department of Nutrition, Medical Research Institute Kitano Hospital, PIIF Tazuke- Kofukai, Osaka, [3]Department of Anesthesiology and Critical Care Hiroshima University, Hiroshima, [4]Diabetes Therapeutics and Research Center, Tokushima University, Tokushima

**These authors contributed equally.*

Abstract : Objective ; In order to maintain a patient's adequate nutritional status, it is important to accurately assess energy expenditure and to provide nutritional administration commensurate with that expenditure. In this study, we have assessed the resting energy expenditures (REE) in patients with esophageal and head and neck cancer, and association between REE, metabolites, nutritional intake, and body composition. Methods ; Patients included in the study had to be diagnosed with esophageal and head and neck cancer, and hospitalized and receiving chemotherapy. REE was measured using indirect calorimetry with a mask and calculated using 3 different equations. Result ; Patients with esophageal and head and neck cancer (67.1 ± 8.5 years old, n=52, all patients were male) were enrolled. The average of REE measured by indirect calorimetry were 22.1kcal/kg/day. REE was positively correlated with muscle mass, body cell mass, and lean body mass. REE was higher in group with oral intake of more than 72%. Blood levels of lactate, pyruvate, and amino acids were higher in cancer patients with esophageal and head and neck cancer compared to healthy subjects. Conclusion : REE measured by indirect calorimetry correlated with the estimated BEE. There was an association between energy expenditure and muscle mass and nutritional intake. J. Med. Invest. 72 : 252-259, August, 2025

Keywords **:** *resting energy expenditures (REE), esophageal cancer, head and neck cancer, metabolite, indirect calorimetry*

INTRODUCTION

In cancer patients undergoing chemotherapy, weight loss due to side effects can significantly affect the continuation of treatment and prognosis (1). Therefore, minimizing weight loss is an important aspect of cancer treatment. In particular, treatment of head and neck cancer and esophageal cancers can significantly affect food intake, resulting in malnutrition (2). Although cancer is generally associated with increased energy expenditure, the extent of energy excess or deficiency remains unclear. This uncertainty arises from a complex interplay of opposing factors - insufficient energy intake and increased energy consumption promote energy deficiency, while reduced physical activity and inadequate dietary intake may suppress energy expenditure.

Cancer reprograms metabolism, playing a crucial role in tumor development and progression (3). Unlike normal differentiated cells, which primarily rely on oxidative phosphorylation for adenosine (ATP) production, cancer cells predominantly utilize glycolysis even in the presence of sufficient oxygen - a phenomenon known as aerobic glycolysis or the Warburg effect (4). However, how this metabolic alteration affects the overall energy expenditure of cancer patients remains an open question.

There is a well-established relationship between stress and metabolism (5). Acute and chronic stress are frequently associated with metabolic disturbances (6). In mouse models, all types of stress have been shown to increase energy expenditure (7). However, chronic stress, in particular, leads to weight gain, reduced locomotor activity, and altered fuel utilization (8). Carbohydrates were the predominant fuel in chronic stress exposure, whereas fatty acids were catabolized in acutely and repeatedly restrained animals (8). On the other hand, in human, Langius *et al*. reported that head and neck cancer patients showed normal REE before radiotherapy and during radiotherapy, REE decreased continuously with ongoing weight loss (9). However, weight loss is not the only factor that can explain energy expenditure ; various factors could be exist, including changes in skeletal muscle mass and dietary intake.

In order to maintain a patient's adequate nutritional status, it is important to accurately assess energy expenditure and to provide nutritional administration commensurate with that expenditure (10).Therefore, in this study, we aimed to assess the resting energy expenditures (REE) and the association between REE, metabolites, nutritional intake, and body composition for adequate nutritional administration.

SUBJECT AND METHODS

Study Design and Patients

This study was approved by the Ethics Committee of Tokushima University (approval number : 2748). Eligible participants were inpatients diagnosed with head and neck cancer or esophageal cancer who had undergone chemotherapy in general wards. Inclusion criteria were patients who were 20 years old and over and provided prior informed consent. To account for differences

Received for publication February 19, 2025 ; accepted February 25, 2025.

Address correspondence and reprint requests to Rie Tsutsumi, PhD, Department of Anesthesiology and Critical Care, Graduate School of Biomedical and Health Sciences, Hiroshima University, 734-8551, Japan and Fax : +81-82-257-5269. E-mail : rietsu@hiroshima-u.ac.jp

in body size and metabolism between the sexes, this study only analyzed data from male patients.

Criteria excluded : 1) Patients who have a pacemaker or other medical device in their body that prevents BIA measurement and 2) Patients who are unable to take meal orally due to severe mouth ulcers or taste disorders. 3) Cachexic patients with severe anorexia and weight loss.

Measurement of energy expenditure

Energy expenditure was measured by indirect calorimetry. Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured using a Datex- Ohmeda S/5 monitor (GE Healthcare, UK) equipped with the gas module E-CAiOVX (GE Healthcare, UK) (11). Oxygen concentrations were measured by magnetic pressure oxygen analysis and carbon dioxide concentrations by infrared absorption spectrometry. Energy expenditure (EE) was automatically calculated from these results and minute ventilation rate. The accuracy of VO_2 and VCO_2 measurements was ± 10% (measurement range 20 to 1,000 ml/min).

EE was automatically calculated using the following equation.

$$EE = 5.5 \times VO_2 + 1.7 \times VCO_2 - 18.25 \text{ (Elwyn's formula)}$$

Measurements were taken over 20 minutes, and the average value was automatically stored every minute. The values during the first 2-3 minutes after the start of measurement, when data were not stable, and values in which EE fluctuated greatly due to seizures and atrial fibrillation were excluded, and other values were averaged.

Estimated basal or resting energy expenditure was calculated using the Harris-Benedict formula, based on the height measured on admission, weight measured on the morning of the day of EE measurement (actual weight), and standard weight.

Harris-Benedict formula for male ;
$BEE = 66.473 + 13.7516 \times (W) + 5.0033 \times (H) - 6.755 \times (A)$

Mifflin-St Jeor equation for male (12) ;
$BEE = (10 \times W) + (6.25 \times H) - (5 \times A) + 5$
and multiplied by scale factor for activity level (REE).

NIBIOHN formula for male (13) ;
$(0.1238+(0.0481\times W)+(0.0234\times H)-(0.0138\times A)-0.5473x1)\times 1000/4.186$

BEE ; basal energy expenditure, W : Weight (kg) H : Height (cm) A : Age (years)

We also compared the basal metabolic rate estimated by BioScan 920-II (MP Japan. K.K., Tokyo, Japan), which estimates basal metabolic rate by entering age, height, weight, and sex and measuring BIA.

Comparison of plasma metabolite between cancer patients and healthy subjects

As we previously reported (14), serum samples were mixed with 1 mL of methanol for LC/MS analysis, containing 1 μL of internal standard solution 1 (Agilent Technologies, Tokyo, Japan), 1 mL of chloroform for LC/MS analysis, and 400 μL of distilled water. The mixture was stirred for approximately 30 seconds and then centrifuged at 2,150 × g for 5 minutes at 4°C. The resulting aqueous layer was washed and transferred onto an ultrafiltration filter (Ultrafree MC-PLHCC 250/pk for Metabolome Analysis ; Agilent Technologies). The aqueous layer was then aliquoted onto the ultrafiltration filter after washing and centrifuged at 9,100 × g for 4 hours at 4°C. Following centrifugation, the filter cup was removed. The collection tubes were dried in a centrifugal dryer with the lid open for 2 hours and stored at -80°C until analysis. CE-TOFMS (Agilent Technologies, Inc.) was used for analysis. Immediately prior to analysis, three sample tubes were reconstituted in 50 μL of distilled water with internal standard solution 3 (Agilent Technologies). The data of healthy subjects were used as control. The sample of 12 healthy subjects was extracted from previous study (15) of male subjects aged 50 to 60 years (58.7± 1.2 years old, BMI 22.1 ± 2.8 kg/m^2).

Nutritional Management and evaluation items

A uniform diet was prepared and distributed by the hospital canteen. The recommended daily caloric intake was set at 2,000 kcal with 60 g of protein. The food intake rate was recorded by the patients themselves by dividing the meal into staple, main, and side dishes, and also by nurses or dietitians, and was calculated by checking the consistency of both records. Data collection included the following evaluation items : age, physical measurements, body composition, pre-existing medical conditions, comorbidities, date of cancer diagnosis, cancer type, histopathological classification, clinical stage, details of the first course of chemotherapy and antiemetic therapy, use of antiemetic drugs, blood biochemical tests and dietary intake. Body composition was analyzed using the BIA method (InBodyS10, InBody, Tokyo, Japan), and nutritional intake was assessed through daily food records.

Statistical Analysis

Data were presented as numbers (%) or mean ± standard deviation. Between-group comparisons were conducted using Kruskal-wallis test. Univariate analysis was performed to assess the association of measured REE and estimated EE, and to identify factors for energy expenditure using Spearman's correlation coefficient and logistic regression analysis. Data analyses were conducted using JMP version 13.1.0 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

RESULTS

Patients' characteristics

A total of 52 patients participated in the study (100% male, 36 patients with esophageal cancer and 16 patients with head and neck cancer). As shown in Table 1, mean age were 67.7 ± 6.3 years old in patients with esophageal cancer and 65.0 ± 10.2 years old in patients with head and neck cancer. The mean BMI were 21.7 ± 2.9 kg/m^2 in patients with esophageal cancer and 22.8 ± 2.9 kg/m^2 in patients with head and neck cancer. Measured REE was 22.5 ± 4.2 kcal/kg/day in patients with esophageal cancer and 19.6 ± 2.9 kcal/kg body weight in patients with head and neck cancer.

REE measurements

Next, we compared the measured REE values measured by indirect calorimetry with the estimated basal energy expenditure (BEE) based on the Harris-benedict formula, the basal metabolic reference value, the basal metabolic rate estimated by a body composition analyzer, and the basal metabolic rate calculated by the National Institute of Health and Nutrition using doubly labeled water. As shown in Figure 1-A, the REE in cancer patients was similar to the BEE estimates obtained by other calculation formulas, and there was no hypermetabolism due to cancer. In addition, the REE measured by indirect calorimetry correlated with the estimated BEE using the Harris-benedict formula (Fig. 1B, $r=0.719$, $p<0.01$).

Table 1. Patients Characteristics

	Total	Esophageal cancer	Head and Neck Cancer
	n = 52	n = 36	n = 16
Age (years) (mean ± SD)	67.1 ± 8.5	67.7 ± 6.3	65.0 ± 10.2
BMI (kg/m^2)	22.3 (20.4-23.8)	21.7 (20.4-22.1)	22.8 (20.6-23.8)
REE (kcal/kg/day)	22.1 (17.1-24.1)	22.5 (20.1-23.9)	19.6 (17.1-24.1)
Stage			
Stage I , n (%)	1 (1.9)	0 (0)	1 (6.3)
Stage II , n (%)	3 (5.8)	2 (5.6)	1 (6.3)
Stage III , n (%)	40 (77.0)	28 (77.8)	12 (75.0)
Stage IV , n (%)	8 (15.4)	6 (16.7)	2 (6.5)
Co-morbidity			
Hypertension, n (%)	8 (15.4)	6 (16.7)	2 (6.5)
Diabetes, n (%)	4 (7.7)	2 (5.6)	2 (6.5)
Dyslipidemia, n (%)	9 (17.3)	5 (13.9)	4 (13.0)
Liver disease, n (%)	1 (1.9)	1 (2.3)	0 (0)
Hyperuricemia, n (%)	2 (3.8)	1 (2.3)	1 (6.3)
Renal failure, n (%)	2 (3.8)	1 (2.3)	1 (6.3)

BMI ; body mass index, REE ; resting energy expenditure

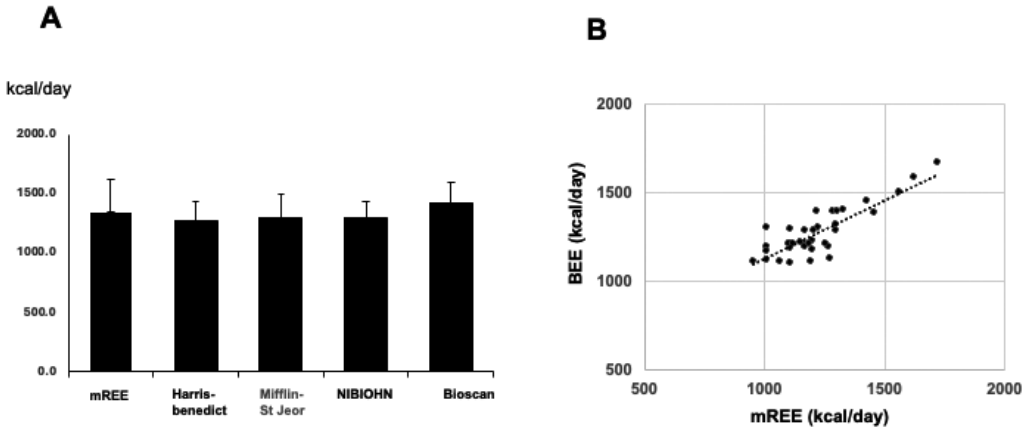

Figure 1. REE in patients with esophageal and head and neck cancer
A ; comparison of REE estimated by several methods. mREE ; measured resting energy expenditure using indirect calorimetry. Harris-Benedict ; estimated basal energy expenditure by Harris-Benedict formula. Mifflin-St Jeor ; estimated basal energy expenditure by Mifflin-St Jeor equation. NIBIOHN ; basal metabolic rate established by NIBIOHN (National Institutes of Biomedical Innovation, Health and Nutrition) multiplied by reference weight. Bioscan ; estimated basal energy expenditure by BIA analyzer Bioscan. N=52
B ; Correlation between mREE and BEE. mREE ; measured resting energy expenditure using indirect calorimetry. BEE ; estimated basal energy expenditure by Harris-Benedict formula. Spearman correlation test, r= 0.719, p<0.01

Comparison of plasma metabolite between cancer patients and healthy subjects

We next performed metabolomic analysis of plasma to investigate the metabolic dynamics of the patients. Metabolite concentrations were analyzed in plasma from cancer patients matched for age and BMI to healthy men (58.7 ± 1.2 years old, BMI 22.1 ± 2.8 kg/m^2) in this study. As shown in Figure 2A-B, cancer patients had significantly higher lactate and pyruvate levels than healthy controls, suggesting significant ATP production by the glycolytic pathway (lactate ; 11095.5 ± 7072 vs 190130.2 ± 287, $p < 0.01$, pyruvate ; 123.8 ± 68.2 vs 344.7 ± 44.5, $p < 0.05$).

In addition, metabolomic analysis of plasma showed that cancer patients had significantly higher levels of free amino acids compared to healthy controls, suggesting the possibility of skeletal muscle degradation (Figure 2C)

Effects of Body Composition and Nutritional Intake on REE

We finally examined the effects of body composition and nutritional intake on REE. Data from all 52 patients in this study were analyzed together. As shown in Figure3A-C, free fat mass (FFM), skeletal muscle mass, and body cell mass (BCM) were positively correlated with REE (FFM ; $r = 0.5129$, $p < 0.05$, muscle mass ; $r = 0.4271$, $p < 0.05$, BCM ; 0.4194, $p < 0.05$). Since the mean REE value was 21.3 ± 3.7 kcal/kg/day, patients were divided into two groups by REE value higher or lower than 20 kcal/kg/day, and the high and low REE groups were compared in skeletal muscle mass and BCM. Consistent with Figure 3B-C, skeletal muscle mass and BCM were significantly higher in the high REE group than in the low REE group (Figure 3D-E ; 23.8 (21.6-25.4) kg vs 27.5 (23.2-30.5) kg, $p < 0.05$ in skeletal muscle mass, 27.5 (23.6-29.5) kg vs 31.8 (27.4-33.4) kg in BCM). In addition, we evaluated the association between REE and body compositions using multivariate analysis to assess the determinants of REE. As shown in Table2, skeletal muscle mass and BCM were identified as factors regulating REE in cancer patients, while FFM showed no significant association.

Furthermore, we examined the effects of nutritional intake on REE. Since the median nutrient intake was 1810 (1368-2200) kcal/day, patients were divided into two groups, higher and lower than 1800 kcal/day, and REE was compared. Median caloric intake of low energy intake group was 1542 (1368-1780) kcal/day and that of high energy intake group was 1890 (1800-2200) kcal/day. As shown in Figure 4A, in the low energy intake group, REE average was 26.2 ± 2.3 kcal/kg/day, whereas in the high REE group, the REE was 27.2 ± 2.5 kcal/kg/day ($P = 0.068$). Since energy intake includes oral dietary intake, enteral nutrition, and peripheral infusions, we next examined the effects of infusion volume and oral dietary intake rate The median dose of energetic infusions was 400 kcal/day, so the groups that received more or less than 400 kcal/day were compared, but there was no significant difference in the REE of the two groups (Figure 4B, 23.1 ± 4.5 kcal/kg/day vs 21.2 ± 2.9 kcal/kg/day). The median percentage of oral intake relative to the amount of food provided to each patient (dietary intake rate) was 71.82%, and REEs were compared by dividing them into two groups : those with dietary intake rates higher than 72% and those with lower rates. As shown in Figure 4C, the REE was significantly higher in the high dietary intake group than in the low dietary intake group (Figure 4C, 21.1 ± 3.1 kcal/kg/day vs 24.1 ± 2.8 kcal/kg/day). These results suggest that REE may be dependent on skeletal muscle mass and oral nutrient intake.

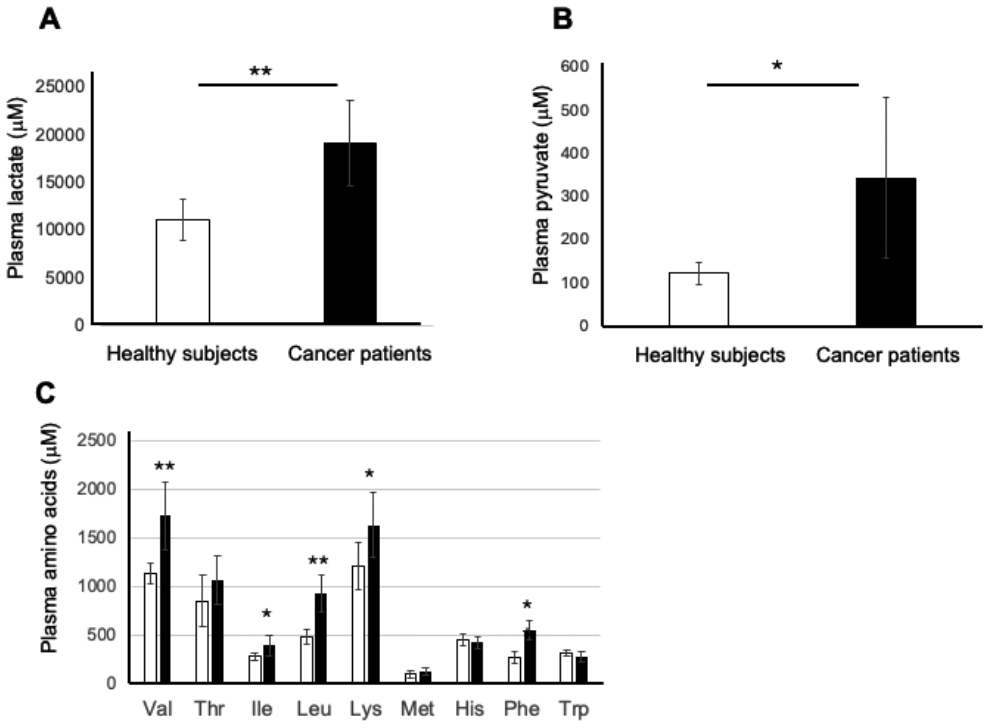

Figure 2. Comparison of plasma metabolite between cancer patients and healthy subjects
A ; Comparison of lactate in cancer patients with esophageal and head and neck cancer (n=52) and healthy subjects (n=12), Wilcoxon rank-sum test, $p < 0.01$
B ; Comparison of pyruvate in cancer patients with esophageal and head and neck cancer (n=52) and healthy subjects (n=12), Wilcoxon rank-sum test, $p < 0.05$
C ; Plasma amino acids concentration in cancer patients with esophageal and head and neck cancer (n=52) and healthy subjects (n=12), Val ; Valine, Thr ; Threonine, Ile ; isoleucine,Lys ; Lysine, Met ; Methionine, His ; Histidine, Phe ; Phenylalanine, Trp ; Trypsin
Wilcoxon rank-sum test, *p<0.05, **p<0.01

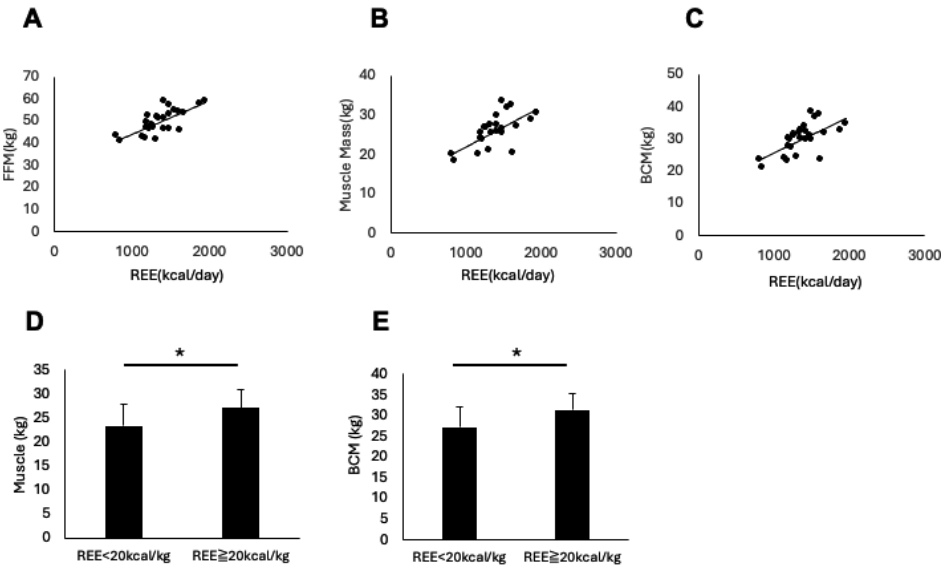

Figure 3. Relationship between REE and Body Composition
A; Correlation between REE and free fat mass (FFM), spearman correlation test, r=0.5129, p<0.05, B; Correlation between REE and skeletal muscle mass, spearman correlation test, r=0.4271, p<0.05, C; Correlation between REE and body cell mass (BCM), spearman correlation test, r=0.4194, p<0.05, D; Comparison of skeletal muscle amount between high and low REE group. Patients were divided into two groups, one with REE less than 20 kcal/kg/day and the other with REE greater than 20 kcal/kg/day, and muscle mass was compared. *p<0.05, E; Comparison of BCM amount between high and low REE group. Patients were divided into two groups, one with REE less than 20 kcal/kg/day and the other with REE greater than 20 kcal/kg/day, and BCM was compared. Wilcoxon rank-sum test, *p<0.05

Table 2. Multivariate analysis to evaluate the association between REE and body compositions

	Model 1		Model 2		Model 3	
	OR (95%CI)	**p-value**	**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**
Skeltal muscle mass (kg)	1.78 (0.98-2.83)	**0.041**	1.65 (0.99-1.92)	**0.048**	1.55 (1.02-1.85)	**0.043**
Free Fat Mass (kg)	1.38 (0.99-1.60)	0.066	1.21 (0.99-1.54)	0.061	1.24 (1.01-1.30)	0.068
Bofy fat (%)	1.06 (0.85-1.35)	0.184	1.10 (0.67-1.30)	0.236	1.06 (0.73-1.53)	0.761
BMI (kg/m^2)	0.53 (0.31-0.91)	0.922				
BCM (kg)			1.45 (1.01-1.69)	**0.035**		
ECW/TBW					0.40 (0.19-1.12)	0.998

BMI ; body mass index, BCM ; body cell mass, ECW/TBW ; extracellular water/total body water

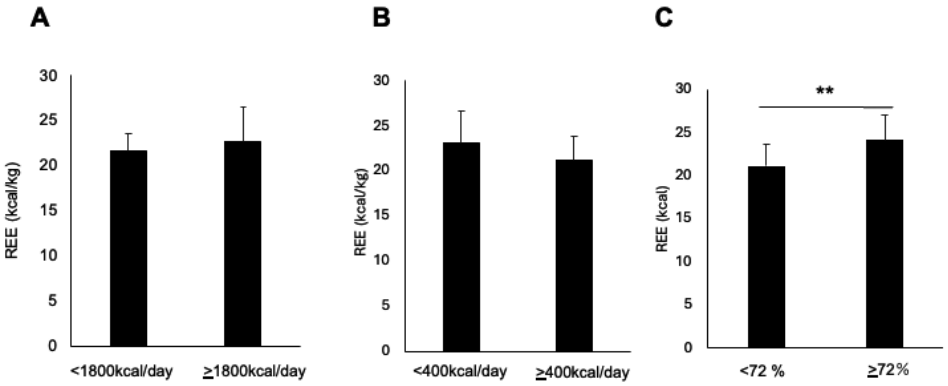

Figure 4. Relationship between REE and Nutritional Intake
A; Patients were divided into two groups, one with energy intake less than 1800 kcal/day and the other with energy intake greater than 1800 kcal/day, and REE was compared. Wilcoxon rank-sum test, n.s, B ; Patients were divided into two groups, one with peripheral infusions less than 400 kcal/day and the other with energy intake greater than 400 kcal/day, and REE was compared. Wilcoxon rank-sum test, n.s. B ; Patients were divided into two groups, one with an oral intake rate of less than 72% and the other with oral intake rate greater than 72%, and REE was compared. Wilcoxon rank-sum test,

DISCUSSION

In the present study, we have measured REE in esophageal and head and neck cancer patients undergoing chemotherapy, and the measured REE and BEE values calculated by the estimation equation were close and positively correlated with muscle mass, BCM, and lean body mass. In addition, metabolites of lactate, pyruvate, and amino acids were higher in cancer patients than in healthy controls. In addition, REE may be dependent on skeletal muscle mass and oral nutrient intake.

We included elderly head and neck patients and esophageal cancer patients who spend more time lying down during the day and found that the measured REE did not differ significantly from the estimated basal metabolic rate, which had previously been calculated by the estimation equation. In other words, REEs were not significantly increased in patients with low activity, suggesting that there is no need to consider the increase in consumption due to invasive procedures for basal metabolism. Recently, Cioffi *et al*. reported that measured REE was slightly higher in female breast cancer patients compared to healthy controls (16). Considering that the mean age in their study was 49.9 ± 11.1 years and the mean BMI was 24.5 ± 2.8 kg/m^2, younger and higher BMI than the subjects in this study, it may also be important to consider energy metabolism by age and BMI. On the other hand, in the previous report by Zurlo, in a middle-aged male patient who underwent surgery for esophageal cancer, energy expenditure rates were repeatedly measured by indirect calorimetry in both basal state (BMR) and resting feeding state (RMR), and the mean preoperative BMR was 23.7 ± 1.0 kcal/kg. day, whereas the postoperative BMR increased to 27.6 ± 2.7 kcal/kg/day (day 6) and then decreased to 24.4 ± 1.4 kcal/kg/day (day 10) (17). This suggests that while surgical invasion may increase energy expenditure, it may not change significantly under chronic conditions.

The reason for increased energy expenditure in cancer may be due to chronic inflammation as well as surgical invasion. Tumors are chronically inflamed, but not markedly, and the C-reactive protein levels in the study subjects were high and within norms.

Himbert *et al*. reported that obese, physically inactive cancer patients had higher C-reactive protein levels, which may be due to inflammation caused by obesity or suppression of anti-inflammatory mechanisms due to low activity level (18). The fact that no obese patients in this study had a BMI of 30 or higher and that they were not bedridden, although their physical activity levels were low, may explain the lack of significant inflammation. Furthermore, Feng *et al*. reported that REE is negatively correlated with CRP in stroke patients, suggesting an association with inflammatory status (19). Therefore, we believe that the hypermetabolism caused by inflammation was not pronounced. On the other hand, however, it is also known from studies in breast cancer patients that energy expenditure is reduced due to decreased metabolism and physical activity (20). In light of these findings, it is suggested that there are more factors that decrease rather than increase metabolism in cancer patients, and that energy expenditure may never be higher than previously estimated.

Hence, if direct measurement of energy expenditure in cancer patients is not possible, various factors including diet and body composition must be considered. The effect of dietary intake on diet-induced thermogenesis was examined in a study by Weston *et al*. in which indirect calorimetry was used to measure REE and thermogenic response to a test meal in weight-stable and weight-loss groups of gastric cancer patients. In that study, cancer patients with weight loss and with cachexia had significantly lower in total energy and protein intakes, with no significant differences in REE between groups when corrected for metabolic body size and lean body mass. In addition, diet-induced thermogenesis was decreased in patients with weight-reduced cancer. The decrease in diet-induced thermogenesis in weight-loss cancer patients is another component of starvation adaptation following weight loss, suggesting that changes in thermogenesis do not contribute to the weight loss seen in cancer cachexia.

ASPEN guideline suggested that serum albumin and hemoglobin are not ideal indicators of malnutrition since energy expenditure vary greatly among individuals and the serum levels are not affected by only changes of nutrient intake (21). Our study has suggested that REE was not greatly varied by cancer, but nutritional intake affected REE suggesting that REE is more likely to reflect the effects of nutrient intake than blood and biochemical tests such as serum albumin and hemoglobin. The skeletal muscle mass and nutritional intake were the determinants of REE in cancer patients and REE might reflect nutritional status rather than blood and biochemistry data. In this study, among body composition, skeletal muscle mass and BCM had a significant effect on REE. The relationship of skeletal muscle mass to REE was clearer than that of free fat mass, which is generally recognized, perhaps because of the infusion of fluids during chemotherapy, which is significantly influenced by extracellular water volume. On the other hand, BCM is the cellular component of body composition, the sum of body proteins and intracellular water, and can be regarded as the part of the body that is actively metabolized. BCM is a nutritional indicator that is relatively insensitive to the effects of water and other elements, since it is mostly composed of skeletal muscle. Indeed, in recent studies, it has been used as an indicator of improvement in nutritional status through nutritional intervention (22, 23). Therefore, skeletal muscle mass and somatic cell mass, including only intracellular water, are considered to be important determinants of energy metabolism.

As for metabolite, for example, in gliomas, which are very complex and metabolically active brain tumors, recent report has found altered levels of metabolites in the blood early in tumor development (24). Metabolites associated with early glioma development were found to be associated with increased energy metabolism, as highlighted by increased levels of TCA-related metabolites such as fumarate and malate (25). Metabolites associated with glioma progression at surgery were also found to be primarily metabolites of high levels of amino acids and amino acid catabolism, with elevated levels of 11 amino acids and two branched-chain alpha-keto acids, ketoisine and ketoisoleucine. By examining these blood-based patterns of metabolic progression, Zhu *et al*. demonstrated that this high amino acid turnover is detectable in simple blood samples (26). Tryptophan metabolism via the kynurenine and serotonin pathways has also been reported to significantly affect immune response and tumor progression in colorectal cancer.

Although the energy expenditure in patient with head and neck cancer was confirmed, this study has several limitations. First of all, the sample size of this study was relatively small. Fifty-six patients were enrolled totally but these patients included patients with esophageal cancer and head and neck cancer, each at a different stage and age. In this study, only male subjects were included to exclude differences by gender, but no correction for body size was made. There were also several patients with chronic diseases related to inflammation, such as type 2 diabetes and dyslipidemia, but the effect of the presence or absence of these diseases on REE was not studied due to insufficient enrollment. In addition, only those who were physically fit enough to wear a mask for indirect calorimetry were included. These considerations made it difficult to perform a fully stratified analysis of the 52 subjects, and more cases are needed in the future

to clarify the conclusions. Second, this study is a single-center cross-sectional study. Therefore, all patients included in the study were on chemotherapy, and none were in palliative care or otherwise. In addition, because this was a cross-sectional study, REE was measured only once for each patient, and no relationship with diet or weight change was examined. Furthermore, mREE was not measured in healthy subjects in this study. Therefore, the association between energy expenditure and plasma metabolites could not be adequately examined. Further studies are needed examine the relationship between REE and metabolites in various conditions, including healthy subjects and cachexia patients. Despite these limitations, however, our study provided valuable insights into the actual energy expenditure of cancer patients.

In cancer patients, administration of less than energy expenditure leads to undernutrition, which can lead to complications of infection and poor prognosis. On the other hand, excessive nutritional intake that does not match energy expenditure can also lead to excess fat accumulation and associated increased inflammation, especially in conditions of inadequate physical activity (27). Therefore, understanding the actual status of energy consumption and administering appropriate energy may contribute to patient prognosis. In this study, we found that energy expenditure is never increased in cancer patients and that energy expenditure is influenced by body composition, particularly muscle mass and oral nutrient intake. Further studies will contribute to improving patient prognosis by adjusting energy requirements according to individual body composition and nutritional intake.

DECLARATION OF INTEREST

none

ACKNOWLEDGEMENTS

We thank the nurses and doctors at Department of Otolaryngology and Department of Thoracic, Endocrine Surgery and Oncology, the Tokushima University Hospital for their cooperation.

REFERENCE

1. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, Baptista G, Barazzoni R, Blaauw R, Coats A, Crivelli A, Evans DC, Gramlich L, Fuchs-Tarlovsky V, Keller H, Llido L, Malone A : GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. Clin Nutr 38 : 1-9, 2019, doi : 10.1016/j.clnu.2018.08.002.
2. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, Erickson N, Laviano A, Lisanti MP, Lobo DN, McMillan DC, Muscaritoli M, Ockenga J, Pirlich M, Strasser F, de van der Schueren M, Van Gossum A, Vaupel P, Weimann A : ESPEN expert group recommendations for action against cancer-related malnutrition. Clin Nutr 36 : 1187-1196, 2017, doi : 10.1016/j.clnu.2017.06.017.
3. Guo ZX, Ma JL, Zhang JQ, Yan LL, Zhou Y, Mao XL, Li SW, Zhou XB : Metabolic reprogramming and immunological changes in the microenvironment of esophageal cancer : future directions and prospects. Front Immunol 16 : 1524801, 2025, doi : 10.3389/fimmu.2025.1524801.
4. Koppenol WH, Bounds PL, Dang CV : Otto Warburg's contributions to current concepts of cancer metabolism. Nat Rev Cancer 11: 325-337, 2011, doi : 10.1038/nrc3038.
5. Feng J, Wang L, Yang X, Chen Q : The systemic oxidative stress index predicts clinical outcomes of esophageal squamous cell carcinoma receiving neoadjuvant immunochemotherapy. Front Immunol 16 : 1535507, 2025, doi : 10.3389/fimmu.2025.1535507.
6. Schweiger U, Laessle R, Schweiger M, Herrmann F, Riedel W, Pirke KM : Caloric intake, stress, and menstrual function in athletes. Fertil Steril 49 : 447-450, 1988, doi : 10.1016/s0015-0282(16)59771-4.
7. Abdullahi A, Chen P, Stanojcic M, Sadri A.R, Coburn N, Jeschke MG : IL-6 Signal From the Bone Marrow is Required for the Browning of White Adipose Tissue Post Burn Injury. Shock 47 : 33-39, 2017, doi : 10.1097/SHK.0000000000000749.
8. Kuti D, Winkler Z, Horvath K, Juhasz B, Szilvasy-Szabo A, Fekete C, Ferenczi S, Kovacs KJ : The metabolic stress response : Adaptation to acute-, repeated- and chronic challenges in mice. iScience 25 : 104693, 2022, doi : 10.1016/j.isci.2022.104693.
9. Langius JA, Kruizenga HM, Uitdehaag BM, Langendijk JA, Doornaert P, Leemans CR, Weijs PJ : Resting energy expenditure in head and neck cancer patients before and during radiotherapy. Clin Nutr 31 : 549-554, 2012, doi : 10.1016/j.clnu.2011.12.009.
10. Steer B, Loeliger J, Edbrooke L, Deftereos I, Laing E, Kiss N : Malnutrition Prevalence according to the GLIM Criteria in Head and Neck Cancer Patients Undergoing Cancer Treatment. Nutrients 12 : 2020, doi : 10.3390/nu12113493.
11. Stapel SN, Weijs PJM, Girbes ARJ, Oudemans-van Straaten HM : Indirect calorimetry in critically ill mechanically ventilated patients : Comparison of E-sCOVX with the deltatrac. Clin Nutr 38 : 2155-2160, 2019, doi : 10.1016/j.clnu.2018.08.038.
12. Karagun B, Baklaci N : Comparative analysis of basal metabolic rate measurement methods in overweight and obese individuals : A retrospective study. Medicine (Baltimore) 103 : e39542, 2024, doi : 10.1097/MD.0000000000039542.
13. Ganpule AA, Tanaka S, Ishikawa-Takata K, Tabata I : Interindividual variability in sleeping metabolic rate in Japanese subjects. Eur J Clin Nutr 61 : 1256-1261, 2007, doi : 10.1038/sj.ejcn.1602645.
14. Okamatsu-Ogura Y, Kuroda M, Tsutsumi R, Tsubota A, Saito M, Kimura K, Sakaue H : UCP1-dependent and UCP1-independent metabolic changes induced by acute cold exposure in brown adipose tissue of mice. Metabolism 113 : 154396, 2020, doi : 10.1016/j.metabol.2020.154396.
15. Tsutsumi R, Yamasaki Y, Takeo J, Miyahara H, Sebe M, Bando M, Tanba Y, Mishima Y, Takeji K, Ueshima N, Kuroda M, Masumoto S, Harada N, Fukuda D, Yoshimoto R, Tsutsumi YM, Aihara KI, Sata M, Sakaue H : Long-chain monounsaturated fatty acids improve endothelial function with altering microbial flora. Transl Res 237 : 16-30, 2021, doi : 10.1016/j.trsl.2021.03.016.
16. Cioffi I, Di Vincenzo O, Morlino D, Ramos da Silva B, Prado CM, Santarpia L, Scalfi L, Giuliano M, De Angelis C, Pasanisi F, Arpino G, Marra M : Measurement of resting energy expenditure and its accuracy in women with breast cancer. Clin Nutr 43 : 54-64, 2024, doi : 10.1016/j.clnu.2024.09.037.
17. Zurlo F, Schutz Y, Pichard C, Roulet M, Monnier P, Savary M, Jequier E : What energy level is required to avoid nutrient depletion after surgery in oropharyngeal cancer? ORL J Otorhinolaryngol Relat Spec 50 : 236-245, 1988, doi : 10.1159/000275997.
18. Himbert C, Warby CA, Gigic B, Ose J, Lin T, Viskochil

R, Peoples AR, Ashworth A, Schrotz-King P, Scaife CL, Cohan JN, Jedrzkiewicz J, Schirmacher P, Grady WM, Cohen SA, Krane M, Figueiredo JC, Toriola AT, Siegel EM, Ulrich CM : Associations of Individual and Combined Physical Activity and Body Mass Index Groups with Proinflammatory Biomarkers among Colorectal Cancer Patients. Cancer Epidemiol Biomarkers Prev 31 : 2148-2156, 2022, doi : 10.1158/1055-9965.EPI-22-0681.

19. Feng H, Pan H, Yao W, Mei C : Analysis of Resting Energy Consumption and Its Influencing Factors in Stroke Patients with Severe Neurological Diseases : A Retrospective Clinical Study. Neuroimmunomodulation 29 : 460-467, 2022, doi : 10.1159/000524719.
20. Demark-Wahnefried W, Hars V, Conaway MR, Havlin K, Rimer BK, McElveen G, Winer EP : Reduced rates of metabolism and decreased physical activity in breast cancer patients receiving adjuvant chemotherapy. Am J Clin Nutr 65 : 1495-1501, 1997, doi : 10.1093/ajcn/65.5.1495.
21. Taylor BE, McClave SA, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice TW, Cresci GA, Gervasio JM, Sacks GS, Roberts PR, Compher C : Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient : Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). Crit Care Med 44 : 390-438, 2016, doi : 10.1097/CCM.0000000000001525.
22. Peng J, Xiang Y, Liu G, Ling S, Li F : The early prognostic value of the 1-4-day BCM/PA trend after admission in neurocritical patients. Sci Rep 14 : 21802, 2024, doi : 10.1038/s41598-024-72142-3.
23. Annunziata G, Verde L, D'Orsi V, Caprio M, Gorini S, Savastano S, Colao A, Muscogiuri G, Barrea L : Supplementation with essential amino acids in the early stage of carbohydrate reintroduction after a very-low energy ketogenic therapy (VLEKT) improves body cell mass, muscle strength and inflammation. J Transl Med 23 : 111, 2025, doi : 10.1186/s12967-024-06037-2.
24. Loding S, Andersson U, Kaaks R, Schulze MB, Pala V, Urbarova I, Amiano P, Colorado-Yohar SM, Guevara M, Heath AK, Chatziioannou AC, Johansson M, Nyberg L, Antti H, Bjorkblom B, Melin B : Altered plasma metabolite levels can be detected years before a glioma diagnosis. JCI Insight 8 : 2023, doi : 10.1172/jci.insight.171225.
25. Loding S, Antti H, Sjoberg RL, Melin B, Bjorkblom B : Blood based metabolic markers of glioma from pre-diagnosis to surgery. Sci Rep 14 : 20680, 2024, doi : 10.1038/s41598-024-71375-6.
26. Zhu M, Hu Y, Gu Y, Lin X, Jiang X, Gong C, Fang Z : Role of amino acid metabolism in tumor immune microenvironment of colorectal cancer. Am J Cancer Res 15 : 233-247, 2025, doi : 10.62347/ZSOO2247.
27. Van Soom T, Tjalma W, El Bakkali S, Verbelen H, Gebruers N, van Breda E : Perspective : Towards Personalised Metabolic Coaching in Cancer. Facts Views Vis Obgyn 10 : 125-130, 2018