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The Relationship between Energy Expenditure and Type or Stage of Cancer

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Malnutrition commonly occurs in patients with cancer. This situation can be associated with increased morbidity and mortality. The etiology is not clearly understood but decreased energy intake and increased energy expenditure may be involved. We aimed to investigate the energy metabolic status including energy expenditure in patients with various cancers. The clinical features and energy metabolic status measured by indirect calorimetry of 74 patients with cancer (50 men and 24 women; mean age, 64.7 years) were obtained from the medical records. Hypermetabolism was more common and REE/kg (resting energy expenditure / kg body weight) seems to be more reliable in estimating the true energy expenditure than %REE (measured REE / predicted REE). The REE/kg and VO_2/kg (oxygen consumption per minute / kg body weight) varied among cancer types, i.e., they were significantly higher in gastric cancer than in hepatocellular carcinoma. Moreover, REE/kg and VO_2/kg was significantly higher in cancer stage IV than in stage I, or stages I and II. Patients with or at risk for malnutrition should receive appropriate nutritional support, which has to be personalized according to tumor site, tumor stage, and the nutritional status of the patient. This nutritional support should improve not only the patients' quality of life but also their survival.

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Introduction

Progressive deterioration of nutritional status is frequently seen in patients with cancer. This is often referred to as cachexia, which is associated with negative outcomes including increased morbidity, poor prognosis, poor tolerance to treatment, and decreased quality of life. The etiology of cachexia is not clearly understood but is thought to be multifactorial, including decreased energy intake (mainly due to anorexia) and increased energy expenditure (metabolic alterations caused by the tumor burden or the host).[1-3] However, it is unclear whether the presence of cancer causes an increased energy demand in the patient.[4]

Nutritional intervention for patients with cancer can decrease the degree of invasion to non-cancerous tissues, normalize metabolic abnormalities, and promote immune function.[5] Therefore, patients with or at risk for malnutrition should receive appropriate nutritional support, which has to be personalized according to tumor site, tumor stage, the nutritional status of the patient, the toxicity of the respective therapy, and the influence of symptoms on the daily eating requirements.[3]

Appropriate energy and nutritional support recommendations for patients with cancer should be based on an energy expenditure estimation.[6] Indirect calorimetry is a method commonly used to assess such an energy expenditure esti-

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mation and represents a chemical method for determining the amount of heat released from a subject rather than a physical method such as direct calorimetry.[4] This chemical method has the advantages of being precise, reproductive, safe, noninvasive, portable, and rapid in making measurements, despite being expensive and requiring training to use.[6,7]

In the present study, we aimed to investigate the energy metabolic status, including energy expenditure, in patients with various (mainly gastrointestinal and hepatobiliary) cancers.

Patients and Methods

Patients

The participants in the present study were 74 patients with cancer (50 men and 24 women; mean age, 64.7 ± 12.4 years) who were admitted to the Department of Gastroenterology and Hepatology, Nagasaki University Hospital, Japan, and who also underwent indirect calorimetry between April 2008 and October 2009. Of the 74 patients with cancer, 7 had been given a diagnosis of esophageal cancer, 20 gastric cancer, 4 colorectal cancer, 37 hepatocellular carcinoma, 3 pancreatic cancer, 2 biliary tract cancer, and 1 lung cancer. The information obtained from the medical records for the present study included sex, age, height, body weight, stage of cancer,[8-14] history of alcohol intake and cigarette smoking, associated disease such as hypertension or diabetes mellitus, peripheral white blood cell count (WBC), lymphatic cell count (Ly), hemoglobin (Hb), and serum levels of total protein (TP), albumin (Alb), total cholesterol (TC), blood urea nitrogen (BUN), creatinine (Cr), total bilirubin (TB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), c-reactive protein (CRP), sodium (Na), potassium (K), chloride (Cl), and calcium (Ca). Standard biochemical tests were performed on a multichannel autoanalyzer.

The body mass index (BMI) was calculated as body weight (kg) divided by height squared (m^2). The history of alcohol intake was divided into two groups as follows: drinker (at least 70 g/day of alcohol intake for more than 5 years) and non-drinker (less than 70 g/day of alcohol intake for up to 5 years). The history of cigarette smoking was divided into two groups as follows: smoker (habitual smoker) and non-smoker.

Indirect calorimetry

Indirect calorimetry was carried out in the morning after overnight bedrest and fasting using a Vmax SPECTRA 29n calorimeter (Cardinal Health 207. Inc., Dublin, OH, USA). The equipment was calibrated at the start of each measurement in accordance with the manufacturer's instructions. About 3 or 4 minutes after the patient was seated in the supine position in a rigid canopy (placed over the head in which the patient respires freely), oxygen consumption per minute (VO_2) and carbon dioxide production per minute (VCO_2) were measured during at least a 15-minute period. Resting energy expenditure (REE) was calculated using the modified Weir formula[15] as follows: REE (kcal/day) = [3.9 x VO_2 (L/min) + 1.1 x VCO_2 (L/min)] x 1440. Respiratory quotient (RQ) was calculated as follows: RQ = VCO_2 (L/min) / VO_2 (L/min). On the other hand, the predicted REE was estimated from the Harris-Benedict equations[16] as follows: basal metabolic rate (BMR) (kcal/day) for men = 66.47 + 13.75 x body weight (kg) + 5.00 x height (cm) - 6.75 x age (year). The BMR (kcal/day) for women = 655.10 + 9.56 x body weight (kg) + 1.85 x height (cm) - 4.68 x age (year). The %REE was calculated as follows: %REE = measured REE (kcal/day) / predicted REE (kcal/day).

Ethical consideration

This study was performed according to the principles of the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of University of Nagasaki. Informed consent was obtained from all participants in Nagasaki University Hospital.

Statistical analysis

Data were expressed as mean ± standard deviation (SD) or as median (range). Correlations between parameters were determined by Spearman's rank correlation coefficient. Differences between groups were tested for statistical significance using the two-tailed Mann-Whitney U-test, Kruskal-Wallis test followed by Bonferroni's multiple comparison test, chi-square test, or Fisher's exact probability test because the data did not represent normal or Bell-shaped distributions. All data analyses were performed using IBM SPSS statistics software, version 17.0 (IBM Co., Somers, NY) on a computer with a Windows operating system. A p -value less than 0.05 was considered statistically significant.

Results

Clinical characteristics of 74 patients with cancer

The clinical features of 74 patients with cancer are shown in Table 1. The mean age of patients was similar in men

Table 1. Clinical characteristics of 74 patients with cancer

Clinical and laboratory findings	
Men/women	50/24
Age (years)	66.5 (25-85)
Origin of cancer	
Esophagus/stomach/colorectum/liver/pancreas/biliary tract/lung	7/20/4/37/3/2/1
Gastrointestine/liver, pancreas, and biliary tract	31/42
Cancer stage (I/II/III/IV)	9/16/18/31
Height (m)	1.63 (1.34-1.78)
Body weight (kg)	58.0 (33.3-89.6)
BMI (kg/m^2)	22.4 (16.5-30.6)
REE (kcal/day)	1252 (766-1926)
REE/kg (kcal/kg/day)	22.4 (16.5-29.7)
%REE	104 (77-137)
RQ	0.83 (0.73-1.20)
VO_2 (L/min)	0.18 (0.11-0.28)
VO_2/kg (mL/kg/min)	3.2 (2.4-4.3)
VCO_2 (L/min)	0.15 (0.09-0.27)
WBC (x10^3/mm^3)	4.8 (1.6-9.1)
Ly (x10^3/mm^3)	1.19 (0.27-3.04)
Hb (g/dL)	11.2 (6.6-17.3)
TP (g/dL)	6.6 (4.6-8.2)
Alb (g/dL)	3.8 (2.1-4.8)
TC (mg/dL)	169 (66-248)
BUN (mg/dL)	15 (6-34)
Cr (mg/dL)	0.77 (0.42-1.41)
TB (mg/dL)	0.8 (0.3-6.0)
AST (IU/L)	32.5 (10-218)
ALT (IU/L)	23.5 (8-201)
CRP (mg/dL)	0.14 (0.01-6.90)
Na (mEq/L)	138.5 (130-143)
K (mEq/L)	4.2 (3.0-5.8)
Cl (mEq/L)	105 (95-113)
Ca (mg/dL)	9.1 (7.9-10.2)
History of alcohol intake (non-drinker/drinker)	38/36
History of cigarette smoking (non-smoker/smoker)	34/40
Hypertension (absent/present)	50/24
Diabetes mellitus (absent/present)	59/15

REE/kg, REE per kg body weight; VO_2/kg, VO_2 per kg body weight. Refer to the text in Patients and Methods section for other abbreviations.
Age, height, body weight, body mass index, metabolic parameters, peripheral blood cell counts, hemoglobin, and serum biochemical parameters are expressed as median (range).

(64.4 ± 11.2 years; range, 25-84 years) and women (66.2 ± 13.6 years; range, 34-85 years). Cancer stage was I in 9 patients, II in 16 patients, III in 18 patients, and IV in 31 patients. Of the 74 patients, 15 (20.3%) revealed a BMI <18.5kg/m^2 and 9 (12.2%) had a BMI ≥25kg/m^2. The %REE was less than 100% in 26 (35.1%) patients and more than 100% in 46 (62.2%).

Correlations between %REE and clinical features

There was a weak positive correlation between %REE and peripheral WBC count (Table 2 and Fig. 1). Also, the %REE in cancer stage III or IV was significantly higher than that in cancer stage I or II (Table 3). The median value

Table 2. Correlation between %REE and clinical features

	Correlation coefficient (r)	*p**
Age (years)	0.167	0.155
Height (m)	0.025	0.834
Body weight (kg)	-0.085	0.473
BMI (kg/m^2)	-0.168	0.153
RQ	0.102	0.385
WBC	0.257	0.027
Ly	-0.198	0.091
Hb	0.102	0.387
TP	0.148	0.207
Alb	0.010	0.931
TC	0.001	0.991
BUN	0.039	0.742
Cr	-0.077	0.512
TB	0.004	0.974
AST	0.002	0.984
ALT	-0.084	0.478
CRP	0.055	0.641
Na	-0.113	0.336
K	-0.054	0.645
Cl	-0.178	0.128
Ca	0.033	0.782

**p* values from Spearman's rank correlation coefficient
Refer to the text in Patients and Methods section for abbreviations.

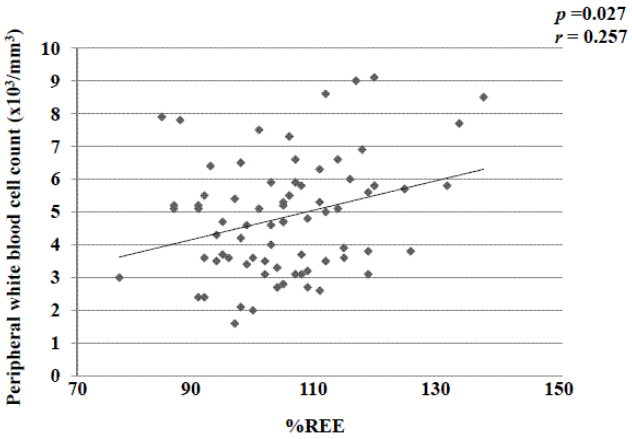

Figure 1. Correlation between %REE and peripheral white blood cell count. A weak positive correlation between %REE and peripheral white blood cell count is shown by Spearman's rank correlation coefficient (r=0.257, p=0.027).
REE, resting energy expenditure. %REE = measured REE (kcal/day) / predicted REE (kcal/day)

Table 3. Correlation between %REE and clinical features (cont'd)

Feature		%REE	*p**
Sex	Men	106 (84-137)	0.061
	Women	99 (77-125)	
Cancer stage	I	102 (84-108)	0.189
	II	99 (86-115)	
	III	106 (90-133)	
	IV	106 (77-137)	
Cancer stage	I/II	101 (84-115)	0.030
	III/IV	106 (77-137)	
History of alcohol intake			
	Non-drinker	102 (77-133)	0.238
	Drinker	106 (84-137)	
History of cigarette smoking			
	Non-smoker	102 (77-133)	0.688
	Smoker	105 (84-137)	
Hypertension	Absent	103 (77-137)	0.071
	Present	104 (90-133)	
Diabetes mellitus			
	Absent	104 (77-137)	0.472
	Present	103 (84-115)	

*p values from two-tailed Mann-Whitney U-test or Kruskal-Wallis test, as appropriate. Refer to the text in Patients and Methods section for abbreviations.
%REE data are expressed as median (range).

of %REE in all patients was 104%. The frequencies of the patients of %REE≤104% was 33.3% (3 out of 9 patients) in stage I, 25.0% (4 out of 16) in stage II, 61.1% (11 out of 18) in stage III, and 67.7% (21 out of 31) in stage IV (p =0.023).

Comparison of clinical features among types of cancer

There were significantly different distributions in cancer stage among cancers. Of the 20 patients with gastric cancer, 16 (80%) had stage IV. All 6 patients with pancreatic, biliary tract, or lung cancers also had stage IV. In contrast, 33 (89.2%) of 37 patients with hepatocellular carcinoma had stages I, II, or III. Body mass index, AST, and TB were significantly higher in cases of hepatocellular carcinoma than in cases of gastric cancer. On the other hand, the REE/kg (REE per kg body weight) and VO_2/kg (VO_2 per kg body weight) were significantly higher in cases of gastric cancer than in cases of hepatocellular carcinoma. White blood cell count and chloride were significantly higher in cases of esophageal cancer than in cases of hepatocellular carcinoma. Chloride was also significantly higher in cases of esophageal cancer than in cases of gastric cancer. The frequency of drinker was significantly higher in patients with esophageal cancer than in patients with pancreatic or biliary tract cancer. There were no significant differences in %REE and RQ among cancers (Table 4).

Comparison of clinical features among cancer stages

All 9 patients with cancer stage I had hepatocellular carcinoma. On the other hand, 16 (51.6%) of 31 patients with cancer stage IV had gastric cancer (Table 5). The REE/kg was significantly higher in cancer stage IV than in cancer stage I (Fig. 2). The VO_2/kg was significantly higher in cancer stage IV than in cancer stages I and II (Fig. 3). There were no significant differences in %REE and RQ among cancer stages (Table 5).

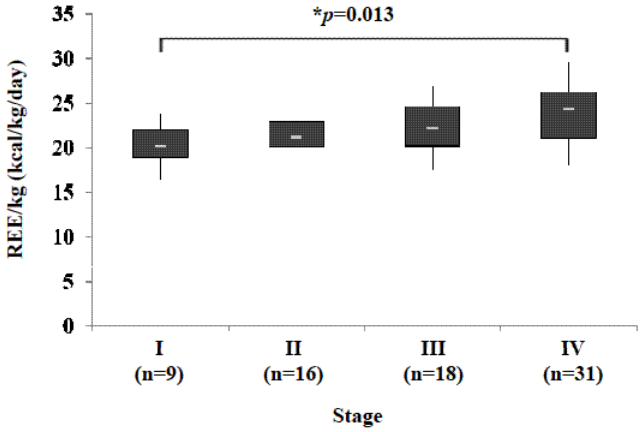

Figure 2. REE/kg in different cancer stages. *Significant difference by Kruskal-Wallis test followed by Bonferroni's multiple comparison test is shown.
REE, resting energy expenditure. REE/kg = REE per kg body weight

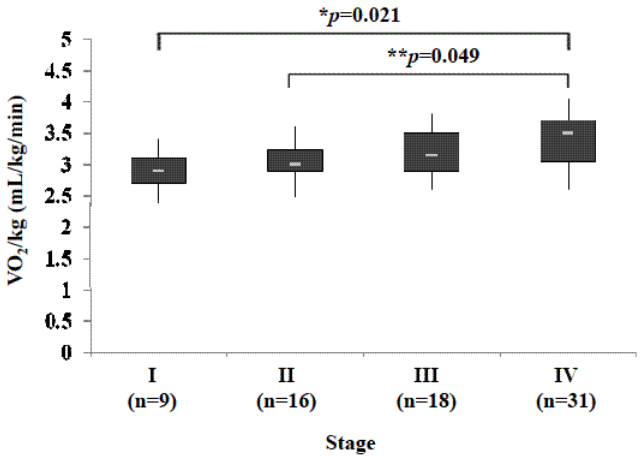

Figure 3. VO_2/kg in different cancer stages.*, **Significant differences by Kruskal-Wallis test followed by Bonferroni's multiple comparison test are shown.
VO_2, oxygen consumption per minute. VO_2/kg = VO_2 per kg body weight

Table 4. Comparison of clinical features among types of cancer except one patient with lung cancer

Feature	Esophageal cancer (n=7)	Gastric cancer (n=20)	Colorectal cancer (n=4)	Hepatocellular carcinoma (n=37)	Pancreatic or biliary tract cancer (n=5)	*p**
Men/women	6/1	10/10	3/1	27/10	3/2	0.336
Age (years)	70(57-75)	61.5(25-79)	65(55-73)	70(43-85)	60(56-79)	0.584
Cancerstage (I/II/III/IV)	0/2/3/2	0/3/1/16	0/0/1/3	9/11/13/4	0/0/0/5	<0.001
Height(m)	1.64(1.59-1.70)	1.62(1.41-1.74)	1.62(1.45-1.72)	1.62(1.34-1.78)	1.67(1.45-1.74)	0.899
Bodyweight(kg)	58.0(52.5-71.2)	48.5(37.4-89.6)	63.0(40.5-69.0)	63.0(33.3-84.8)	53.0(41.7-70.5)	0.056
BMI(kg/m^2)	21.8(19.8-24.6)	19.0(16.5-30.6)	23.1(19.3-25.3)	24.3(16.7-29.4)	20.5(18.8-25.3)	0.006
REE(kcal/day)	1225(999-1770)	1212(932-1926)	1391(766-1736)	1275(825-1897)	1422(969-1592)	0.849
REE/kg(kcal/kg/day)	22.2(19.0-29.7)	24.8(19.0-29.4)	22.0(18.1-26.9)	20.6(16.5-26.0)	23.7(20.7-27.8)	0.001
%REE	103(90-137)	105(86-131)	102(77-133)	102(84-119)	107(97-118)	0.425
RQ	0.79(0.73-0.84)	0.84(0.74-1.20)	0.83(0.81-0.87)	0.83(0.75-1.02)	0.82(0.73-1.00)	0.347
VO_2(L/min)	0.18(0.14-0.26)	0.17(0.14-0.28)	0.20(0.11-0.25)	0.18(0.12-0.26)	0.21(0.14-0.22)	0.761
VO_2/kg(mL/kg/min)	3.2(2.7-4.3)	3.6(2.7-4.2)	3.2(2.6-3.8)	3.0(2.4-3.6)	3.4(3.0-4.1)	0.001
VCO_2(L/min)	0.13(0.11-0.20)	0.15(0.11-0.26)	0.17(0.09-0.20)	0.16(0.10-0.27)	0.15(0.11-0.22)	0.960
WBC(x10^3/mm^3)	6.9(2.7-8.6)	4.9(2.8-7.8)	4.5(3.0-7.7)	3.9(1.6-9.1)	6.5(3.1-9.0)	0.046
Ly(x10^3/mm^3)	1.10(1.02-1.68)	1.36(0.76-3.04)	1.15(0.74-1.48)	1.18(0.38-2.86)	1.20(0.27-1.89)	0.710
Hb(g/dL)	12.2(10.5-13.2)	10.6(8.3-15.4)	12.2(9.3-15.1)	11.3(6.6-17.3)	11.1(8.8-16.1)	0.330
TP(g/dL)	6.6(5.6-7.6)	6.4(4.6-7.1)	6.7(6.2-7.7)	7.0(4.9-8.2)	6.6(5.2-8.2)	0.014
Alb(g/dL)	3.8(3.1-4.3)	3.9(2.3-4.3)	4.2(3.3-4.8)	3.5(2.1-4.8)	3.2(2.4-4.0)	0.094
TC(mg/dL)	194(136-208)	180(122-248)	172(151-220)	159(66-244)	161(118-206)	0.430
BUN(mg/dL)	16(9-27)	14.5(6-34)	14.5(14-16)	15(8-29)	13(11-20)	0.998
Cr(mg/dL)	0.91(0.58-1.05)	0.75(0.53-1.25)	0.78(0.56-0.99)	0.81(0.49-1.41)	0.66(0.57-0.73)	0.266
TB(mg/dL)	0.8(0.3-1.1)	0.55(0.3-1.8)	0.8(0.5-1.5)	0.9(0.4-6.0)	0.6(0.3-1.7)	0.006
AST(IU/L)	18(13-38)	21(10-70)	29.5(22-46)	46(15-218)	28(16-78)	0.004
ALT(IU/L)	12(10-55)	16(8-98)	22(19-33)	34(9-201)	21(12-34)	0.036
CRP(mg/dL)	0.58(0.05-6.90)	0.08(0.01-2.59)	0.05(0.03-1.35)	0.16(0.01-5.86)	0.53(0.09-6.63)	0.122
Na(mEq/L)	137(133-140)	139(131-143)	138(134-140)	138(130-142)	135(134-140)	0.156
K(mEq/L)	4.4(3.5-4.8)	4.2(3.8-5.0)	4.4(4.1-4.7)	4.1(3.0-5.8)	4.4(3.6-4.5)	0.622
Cl(mEq/L)	100(95-104)	105(101-109)	104(101-107)	106(97-113)	104(102-107)	0.017
Ca(mg/dL)	9.3(8.7-9.9)	9.1(8.1-9.7)	9.4(9.2-9.6)	9.0(8.1-10.2)	8.5(7.9-9.3)	0.116
History of alcohol intake (non-drinker/drinker)	1/6	12/8	3/1	17/20	5/0	0.026
History of cigarette smoking (non-smoker/smoker)	2/5	12/8	3/1	13/24	4/1	0.097
Hypertension (absent/present)	3/4	15/5	3/1	24/13	4/1	0.557
Diabetes mellitus (absent/present)	5/2	18/2	4/0	27/10	5/0	0.278

*p values from two-tailed Kruskal-Wallis test, chi-square test, or Fisher's exact probability test, as appropriate. Refer to the text in Patients and Methods section and other tables for abbreviations.

Age, height, body weight, body mass index, metabolic parameters, peripheral blood cell counts, hemoglobin, and serum biochemical parameters are expressed as median (range).

Table 5. Comparison of clinical features among cancer stages

Feature	Stage I (n=9)	Stage II (n=16)	Stage III (n=18)	Stage IV (n=31)	*p**
Men/women	6/3	11/5	15/3	18/13	0.343
Age(years)	71(58-84)	72(25-85)	69.5(47-84)	59(34-79)	0.096
Origin of cancer (Esophagus/stomach/colorectum/liver/pancreas/biliary tract/lung)					
	0/0/0/9/0/0/0	2/3/0/11/0/0/0	3/1/1/13/0/0/0	2/16/3/4/3/2/1	0.001
Height(m)	1.62(1.44-1.70)	1.63(1.47-1.78)	1.62(1.34-1.77)	1.64(1.41-1.74)	0.912
Body weight(kg)	59.6(47.0-73.5)	57.1(36.0-84.8)	62.3(33.3-73.0)	57.2(37.4-89.6)	0.436
BMI(kg/m^2)	24.4(19.0-29.4)	22.3(16.5-28.6)	23.3(18.1-29.0)	21.6(16.9-30.6)	0.300
REE(kcal/day)	1206(1090-1391)	1201(858-1657)	1343(825-1897)	1275(766-1926)	0.269
REE/kg(kcal/kg/day)	20.1(16.5-23.8)	21.2(18.2-25.4)	22.2(17.6-26.9)	24.3(18.1-29.7)	0.013
%REE	102(84-108)	100(86-115)	106(90-133)	106(77-137)	0.189
RQ	0.84(0.75-0.92)	0.85(0.73-0.99)	0.82(0.75-1.02)	0.82(0.73-1.20)	0.803
VO_2(L/min)	0.17(0.16-0.20)	0.17(0.12-0.24)	0.19(0.12-0.26)	0.19(0.11-0.28)	0.276
VO_2/kg(mL/kg/min)	2.9(2.4-3.4)	3.0(2.5-3.6)	3.2(2.6-3.8)	3.5(2.6-4.3)	0.018
VCO_2(L/min)	0.15(0.13-0.16)	0.15(0.10-0.19)	0.16(0.10-0.27)	0.15(0.09-0.26)	0.392
WBC(x10^3/mm^3)	3.5(3.1-7.9)	4.6(1.6-6.0)	5.2(2.4-9.1)	5.1(2.8-9.0)	0.096
Ly(x10^3/mm^3)	1.38(0.46-2.37)	1.22(0.38-1.87)	1.14(0.59-2.86)	1.20(0.27-3.04)	0.879
Hb(g/dL)	13.2(6.6-15.6)	11.4(9.7-15.0)	10.7(9.0-17.3)	11.1(8.3-16.1)	0.510
TP(g/dL)	7.0(5.2-8.2)	6.8(5.6-7.8)	6.8(4.9-7.8)	6.6(4.6-8.2)	0.299
Alb(g/dL)	3.8(2.9-4.4)	3.7(2.3-4.8)	3.5(2.1-4.2)	4.0(2.3-4.8)	0.069
TC(mg/dL)	160(133-212)	160(66-208)	160(89-228)	176(118-248)	0.601
BUN(mg/dL)	14(12-24)	17(9-29)	15(8-34)	14(6-30)	0.285
Cr(mg/dL)	0.76(0.52-1.25)	0.91(0.49-1.41)	0.83(0.56-1.30)	0.68(0.42-1.25)	0.266
TB(mg/dL)	0.8(0.4-2.6)	1.0(0.3-6.0)	0.7(0.3-3.3)	0.6(0.3-1.9)	0.208
AST(IU/L)	53(18-122)	31(17-157)	32.5(13-115)	25(10-218)	0.086
ALT(IU/L)	35(18-115)	27(11-141)	26(9-90)	18(8-201)	0.074
CRP(mg/dL)	0.13(0.01-0.97)	0.10(0.01-3.11)	0.20(0.02-6.90)	0.14(0.01-6.63)	0.580
Na(mEq/L)	140(131-142)	138.5(133-143)	137(130-141)	139(131-142)	0.221
K(mEq/L)	4.2(3.2-5.0)	4.3(3.0-5.8)	4.4(3.8-5.0)	4.1(3.6-5.0)	0.290
Cl(mEq/L)	106(97-109)	106(99-113)	105(95-109)	105(99-108)	0.390
Ca(mg/dL)	9.2(8.2-9.8)	9.0(8.4-10.2)	8.9(8.1-10.0)	9.2(7.9-9.7)	0.716
History of alcohol intake (non-drinker/drinker)	4/5	10/6	6/12	18/13	0.276
History of cigarette smoking (non-smoker/smoker)	5/4	5/11	7/11	17/14	0.380
Hypertension (absent/present)	6/3	7/9	12/6	25/6	0.087
Diabetes mellitus (absent/present)	6/3	11/5	14/4	28/3	0.227

*p values from two-tailed Kruskal-Wallis test, chi-square test, or Fisher's exact probability test, as appropriate. Refer to the text in Patients and Methods section and other tables for abbreviations.

Age, height, body weight, body mass index, metabolic parameters, peripheral blood cell counts, hemoglobin, and serum biochemical parameters are expressed as median (range).

Discussion

Resting energy expenditure represents the amount of calories required by a body for a 24-hour period of inactivity (lying in bed at rest in a comfortable environment).[17] The predicted REE calculated by the Harris-Benedict equations[16] has been widely used to evaluate the energy status of patients. This value is multiplied by activity and stress factors to determine the total energy requirement. Theoretically, the predictive REE is expected to equal the measured REE in healthy persons, and the %REE (measured REE / predicted REE) is a marker for a hypermetabolic status.[18] Inflammatory response may contribute to hypermetabolism and metabolic alterations are often seen in patients with cancer.[6,19] This is in line with our present result of a weak positive correlation between %REE and peripheral WBC count, although CRP was not correlated with %REE.

It is conceivable that REE is increased in patients with cancer because the competition for nutrients between the tumor and the host can lead to an accelerated starvation state that promotes metabolic disturbances (alterations in carbohydrate, lipid, and protein metabolism) in the host, including hypermetabolism, which leads to decreased energy efficiency.[2,20] However, a large span from hypo- to hypermetabolism has been reported in patients with cancer.[1] For example, Macfie et al.[4] reported that gastrointestinal malignancy might result in an increased energy demand, particularly in patients with metastatic disease. Cao et al.[7] also reported that patients with cancer had elevated REE. In contrast, other reports concluded that energy expenditure was not related to the gastric, colorectal, or nonsmall cell bronchial tumor burden,[17,21-23] or was not uniformly hypermetabolic.[24] In our patients, the median value of %REE was 104, and 62.2% of patients revealed %REE≥100%, suggesting that hypermetabolism was more common in patients with cancer.

In our present study, it is noted that REE/kg (REE per kg body weight) was significantly higher in cases of gastric cancer than in cases of hepatocellular carcinoma, and was also significantly higher in cases of cancer stage IV than in cases of cancer stage I. However, there were no significant differences in %REE among cancer types and stages. Johnson et al.[6] reported that Harris-Benedict equations were not suitable for REE prediction in patients with cancer because these equations were intended to assess the basal metabolism rates of healthy persons but sometimes over- or underestimate REE in malnourished patients. Reeves et al.[25] also reported that none of the prediction equations could be adopted for the prediction of individuals' REE within clinical acceptable limits in patients with cancer. Indeed, there tended to be a negative correlation between BMI and cancer stage in our patients, although the correlation was not statistically significant. Harris-Benedict equations consider body weight, but also include nutritionally unrelated factors of height, age, and sex. Therefore, REE/kg seems to be more reliable in estimating the true energy expenditure than %REE (measured REE / predicted REE) in patients with cancer.

The REE/kg and VO_2/kg were significantly higher in cases of gastric cancer than in cases of hepatocellular carcinoma in our present study. Dempsey et al.[26] reported that tumor site was a major determinant of energy expenditure in patients with gastrointestinal cancer, i.e., patients with pancreatic or hepatobiliary tumors tended to be hypometabolic and patients with gastric cancer tended toward hypermetabolism, while approximately half of the patients with esophageal or colorectal neoplasms were normometabolic. Mullen et al.[27] reported that there was a strong positive correlation between the protein synthesis rate of tumor tissue and the normal adjacent tissue from which it arose. Therefore, tumor-protein synthesis, which expends a considerable amount of energy or oxygen, has variable rates that are dependent on the original tumor site. It is noted that almost all of the 37 patients with hepatocellular carcinoma were associated with chronic liver diseases, including liver cirrhosis. Patients with cirrhosis are in a state of protein-energy malnutrition, but the REE results in such patients have remained controversial.[28-30]

Regarding the cancer stage, REE/kg was significantly higher in cases of cancer stage IV than in cases of cancer stage I, and VO_2/kg was significantly higher in cases of cancer stage IV than in cases of cancer stages I and II in the present study. Cao et al.[7] reported that cancer type, pathological stage, and duration of disease influenced REE. However, Fredrix et al.[23] reported that there was no evidence that tumor type (gastric or colorectal) or tumor stage is important in relation to an increase in REE in patients with cancer. In our present study, there was a big limitation because all 9 patients with cancer stage I had hepatocellular carcinoma and more than 50% of patients with stage IV had gastric cancer. Because REE/kg and VO_2/kg were significantly higher in cases of gastric cancer than in cases of hepatocellular carcinoma, the relationship between energy expenditure and cancer stage should have been examined using a single cancer type. Further investigation is needed to confirm this relationship.

In the present study, there may be another limitation because our data were obtained from single-center experience with a small sample size. Multicenter registries have the

advantage over single-center studies of evaluating a large number of patients in a relatively short period of time. However, because of the variability in each center's institutional indirect calorimetry instruments and measurement protocols, interpretation of the results should be carefully interpreted. Further investigation in a single-center with a large sample size is needed to confirm the present findings.

In conclusion, hypermetabolism was more common in patients with cancer, and REE/kg seems to be more reliable in estimating the true energy expenditure than %REE. The REE/kg and VO_2/kg were different among cancer type, i.e., they were significantly higher in cases of gastric cancer than in cases of hepatocellular carcinoma. Moreover, REE/kg and VO_2/kg was significantly higher in cancer stage IV than in cancer stage I, or cancer stages I and II, although there were significantly different distributions in cancer stage among cancer types. Morley et al.[31] suggested that cytokines played a central role in the pathogenesis of cachexia, but adequate and effective nutritional intervention after the accurate energy expenditure estimation could help the improvement of not only the patients' quality of life but also their survival.

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