Investigation of appropriate semi-quantitative index for assessment of esophageal and breast cancer treatment response in Japanese patients using ^{18}F-FDG PET/CT findings

Tatsuya Tsuchitani[1] BS,
Yoshiyuki Takahashi[1] BS,
Yoshihiro Maeda[1] BS,
Masahiko Oda[1] BS,
Takuya Enoki[1] BS,
Noriko Kotoura[1] BS,
Kazuhiro Kitajima[2] MD

1. Department of Radiological Technology, Hyogo College of Medicine College Hospital, Nishinomiya, Hyogo 663-8501 Japan

2. Department of Radiology, Division of Nuclear Medicine and PET Center, Hyogo College of Medicine, Nishinomiya, Hyogo 663-8501 Japan

Keywords: ^{18}F-FDG PET/CT
- PERCIST
- Japanese lean body mass - SULj

Corresponding author:
Kazuhiro Kitajima MD
Department of Radiology, Division of Nuclear Medicine and PET center, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan
1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501 Japan
Phone: + 81-798-45-6883, Fax: + 81-798-45-6262
kazu10041976@yahoo.co.jp

Received:
4 January 2018
Accepted revised :
1 February 2019

Abstract

Objective: To examine the correlation of the quantitative indexes standardized uptake value (SUV), SUV corrected for lean body mass (SUL) and SUV corrected for Japanese lean body mass (SULj) with body weight to develop an appropriate quantitative index independent of body weight fluctuation for assessment of response to cancer treatment in Japanese patients. **Subjects and Methods:** Fifty-six males with esophageal cancer and 30 females with breast cancer underwent fluorine-18-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) scans, once before and once after, receiving neoadjuvant chemotherapy prior to planned surgical resection. The maximum value, peak value, and average value of SUV, SUL and SULj were calculated by setting a spherical volume of interest (3cm diameter) in a normal area of the liver. The correlation between each index and body weight was obtained from the correlation coefficient (r) and the significance of the correlation was tested. **Results:** Analyses were conducted with all patients (P<0.01), as well as after dividing into those with only esophageal (P<0.05) or breast (P<0.01) cancer. Regarding the correlation coefficient between each index and body weight, a significant difference was seen for SUVmax, SUVpeak and SUVmean. In contrast, there was no correlation with body weight for SULmax, SULpeak, SULmean, SULjmax, SULjpeak, or SULjmean in any of the 3 groups. **Conclusion:** Based on the correlation with body weight, we concluded that both SUL and SULj (SUL corrected for Japanese lean body mass) is useful for assessment of cancer treatment response in Japanese patients.

Hell J Nucl Med 2019; 22(1): 20-24 *Epub ahead of print: 7 March 2019* *Published online: 5 April 2019*

Introduction

Integrated positron emission tomography/computed tomography (PET/CT) with fluorine-18-fluoro-2-deoxy-D-glucose (^{18}F-FDG) is a useful technique for acquiring both glucose metabolic and anatomic imaging data using a single device in a single diagnostic session, and has opened up a new field of clinical oncologic imaging. Fluorine-18-FDG PET/CT has been used successfully for the staging, treatment optimization, re-staging, therapy monitoring, and prognostication of various malignant tumors [1-3].

Several indexes, such as maximum standardized uptake value (SUVmax), peak standardized uptake value (SUVpeak), mean standardized uptake value (SUVmean), standardized uptake value corrected for lean body mass (SUL), metabolic tumor volume (MTV) and total lesion glycolysis (TLG), based on ^{18}F-FDG PET/CT findings have become recognized as useful imaging biomarkers to assess treatment effects and prognosis of patients with various types of cancer. SUVmax is the maximum value for pixels included in the set volume of interest (VOI) and SUVpeak is calculated using a 1.2cm diameter VOI placed on the hottest site of the tumor, while SUVmean is the average value for pixels included in the VOI set, SUL is SUV corrected for lean body mass and TLG is the product of SUVmean and MTV.

Although positron emission tomography response criteria in solid tumors (PERCIST) has been proposed for evaluating treatment response in patients with solid cancer as utilization of ^{18}F-FDG PET findings by American researchers in 2009 [4], that uses TLG and SULpeak, the latter of which is SUVpeak corrected for the lean body mass of Western individuals. However, since the calculation of lean body mass is different as compared to Western individuals [5], SULmax, SULpeak, SULmean and PERCIST may not be suitable for Japanese. In recent years, standardized uptake values after correction for Japanese lean body mass (SULj), such as SULjmax, SULjpeak, and SULjmean, have begun to be used for

Japanese individuals with commercially available software, and several studies have been reported regarding evaluation of treatment response in Japanese patients with esophageal cancer, breast cancer and head and neck cancer using SULjpeak and PERCIST [6-9].

To the best of our knowledge, no studies that compared SUL with SULj in Japanese patients have been presented. Here, we examined the correlation between quantitative index values, such as SUV, SUL and SULj, with body weight, to determine an appropriate semi-quantitative index that is not dependent on weight fluctuation for assessment of response to cancer treatment in Japanese patients using ^{18}F-FDG PET/CT findings.

Subjects and Methods

Patients

This was a retrospective analysis of 56 male patients (age 65.0±7.0 years, mean±standard deviation) with esophageal cancer and 30 female patients (52.2±12.4 years) with breast cancer who underwent 2 ^{18}F-FDG PET/CT scans, once before and once after receiving neoadjuvant chemotherapy prior to planned surgical resection. The mean age of all 86 patients was 58.8±11.8 years. This study was approved by our institutional review board.

^{18}F-FDG PET/CT

Whole-body PET/CT scanners were used (Gemini GXL16 and Gemini TF64, Philips Medical Systems, Eindhoven, The Netherlands). The patients were instructed to fast for 5 hours before the examination, then blood glucose was measured immediately before injection of 4.0MBq/kg of body weight of ^{18}F-FDG for the GXL16 or 3.0MBq/kg of body weight ^{18}F-FDG for the TF64. Static emission images were obtained approximately 60 minutes after injection. Attenuation corrected PET images were reconstructed using a line-of-response row-action maximum likelihood algorithm (LOR-RAMLA) (iterations=2, subsets=n/a) for the GXL16 or 3 dimensional-ordered-subsets expectation maximization iterative reconstruction algorithm (3D-OSEM) + time of flight (TOF) (iteration=3, subsets=33) for the TF64. The PET/CT specifications and imaging protocols are shown in Table 1.

Data analysis

We used the commercially available software package GI-PET (AZE Co., Ltd., Tokyo, Japan), which is designed to assist clinicians using PERCIST for monitoring treatment response [6-9]. Since the 2 different PET/CT scanners used in this study may have affected SUV measurements because of the differences between such factors as resolution [10-12], we applied the resolution adjustment function of GI-PET and used a 3D Gaussian filter (8mm) for data obtained by the TF64.

Spherical VOI (3cm in diameter) were placed at 3 locations in a normal area of the liver (Figure 1) by 2 radiology technicians, then the average of the values for those 3 locations was calculated. The indices evaluated in the present study were SUVmax, SUVpeak, SUVmean, SULmax, SULpeak, SULmean, SULjmax, SULjpeak, and SULjmean.

Table 1. *Protocol for PET/CT acquisition and reconstruction with Gemini GXL16 and Gemini TF64.*

	GEMINI GXL16	GEMINI TF64
Crystal	Zr-GSO	LYSO
Crystal size [mm^3]	4×6×30	4×4×22
Reconstruction	LOR-RAMLA	3D-OSEM+TOF
Iterations, Subset	2, n/a	3, 33
Voxel size [mm^3]	4×4×4	4×4×4
Post smoothing filter	n/a	n/a
Dosage [MBq/kg]	4	3
Scan duration [min]	1.5	1.5

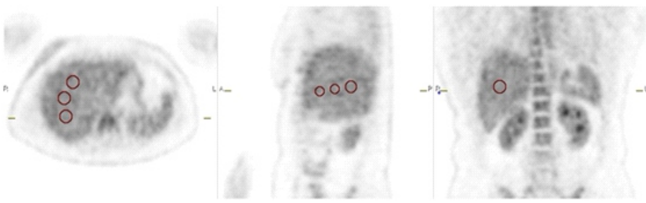

Figure 1. Data analysis. Three spherical VOI (3cm in diameter) were placed in areas of the liver.

Statistical analysis

Using the calculated maximum, peak, and average values for SUV, SUL and SULj, the correlation between each index and body weight was obtained from the correlation coefficient (r) To determine whether the results differed depending on type of cancer or gender, the correlation between each index and body weight was examined after dividing the patients into those with esophageal cancer (males only) and those with breast cancer (females only), as well as for all patients. All statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA), with P values <0.05 considered to indicate significance.

Results

Males with esophageal cancer

Results showing correlations of the maximum, peak, and average values of SUV, SUL and SULj with body weight obtained in 112 PET/CT examinations of 56 male patients with esophageal cancer are shown in Table 2 and Figure 2. Body weight ranged from 38.2 to 88.0kg, with a mean value of 57.3±9.1kg.

Standardized uptake value max showed a significant correlation with body weight (r=0.29, P<0.05), whereas

SULmax (r=0.05, P=0.73) and SULjmax (r=-0.11, P=0.42) did not. Although a significant difference regarding the correlation coefficient (r) between SUVmax and SULjmax was observed (P<0.05), no such significant difference was seen between SUVmax and SULmax (P=0.067), or SULmax and SULjmax (P=0.66). Standardized uptake value peak was also significantly correlated with body weight (r=0.32, P<0.05), whereas SULpeak (r=0.09, P=0.53) and SULjpeak (r=-0.08, P=0.57) were not. There was a significant difference for the correlation coefficient (r) between SUVpeak and SULjpeak (P<0.01), whereas no such significant difference was seen between SUVpeak and SULpeak (P=0.075), or SULpeak and SULjpeak (P=0.21). SUVmean also showed a significant correlation with body weight (r=0.31, P<0.05), whereas SULmean (r=0.11, P=0.41) and SULjmean (r=-0.05, (P=0.71) did not. There was a significant difference regarding the correlation coefficient (r) between SUVmean and SULjmean (P<0.01), whereas that was not seen between SUVmean and SULmean (P=0.12), or SULmean and SULjmean (P=0.24).

***Table 2.** Correlation of SUV, SUL and SULj with body weight in patients with esophageal cancer (males only, n=56).*

	SUV max	SUL max	SUL jmax
Correlation coefficient (r)	0.29	0.05	-0.11
Significance of the correlation	<0.05	0.73	0.42
	SUV peak	**SUL peak**	**SUL jpeak**
Correlation coefficient (r)	0.32	0.09	-0.08
Significance of the correlation	<0.05	0.53	0.57
	SUV mean	**SUL mean**	**SUL jmean**
Correlation coefficient (r)	0.31	0.11	-0.05
Significance of the correlation	<0.05	0.41	0.71

SUVmax; maximum standardized uptake value, SULmax; maximum standardized uptake value corrected for lean body mass, SULjmax; maximum standardized uptake value corrected for Japanese lean body mass, SUVpeak; peak standardized uptake value, SULpeak; peak standardized uptake value corrected for lean body mass, SULjpeak; peak standardized uptake value corrected for Japanese lean body mass, SUVmean; mean standardized uptake value, SULmean; mean standardized uptake value corrected for lean body mass, SULjmean; mean standardized uptake value corrected for Japanese lean body mass, SD; standard deviation

The values of the slope of the regression line for SUVmax, SULmax and SULjmax were 0.0106, 0.0014, and -0.003, respectively, for SUVpeak, SULpeak, and SULjpeak were 0.011, 0.0025, and -0.002, respectively and for SUVmean, SULmean, and SULjmean were 0.0106, 0.0033, and -0.0013, respectively. There was no significant difference between any of the indexes in regard to these values.

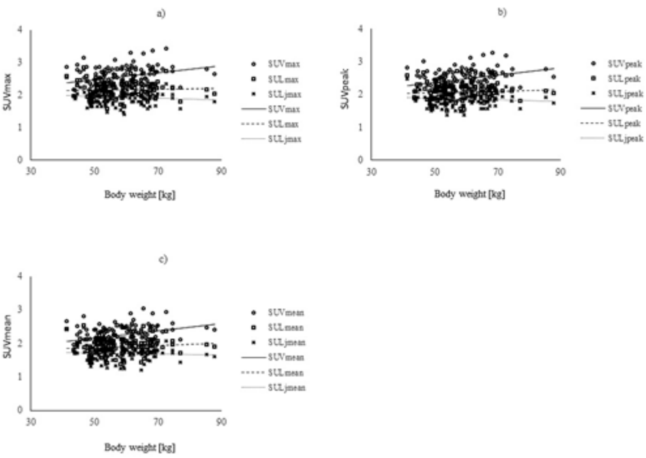

Figure 2. Correlation of SUV, SUL and SULj with body weight in patients with esophageal cancer (males only). a) Max value. b) Peak value. c) Mean value.

Females with breast cancer

Results showing correlations of the maximum, peak, and average values of SUV, SUL and SULj with body weight obtained in 60 PET/CT examinations of 30 female patients with breast cancer are shown in Table 3 and Figure 3. Body weight ranged from 39.9 to 88.4kg, with a mean value of 55.4±9.4kg.

***Table 3.** Correlation of SUV, SUL and SULj with body weight in patients with breast cancer (females only, n=30).*

	SUV max	SUL max	SUL jmax
Correlation coefficient (r)	0.48	0.05	-0.02
Significance of the correlation	<0.01	0.79	0.9
	SUV peak	**SUL peak**	**SUL jpeak**
Correlation coefficient (r)	0.52	0.11	0.04
Significance of the correlation	<0.01	0.56	0.84
	SUV mean	**SUL mean**	**SUL jmean**
Correlation coefficient (r)	0.55	0.15	0.05
Significance of the correlation	<0.01	0.84	0.78

SUVmax; maximum standardized uptake value, SULmax; maximum standardized uptake value corrected for lean body mass, SULjmax; maximum standardized uptake value corrected for Japanese lean body mass, SUVpeak; peak standardized uptake value, SULpeak; peak standardized uptake value corrected for lean body mass, SULjpeak; peak standardized uptake value corrected for Japanese lean body mass, SUVmean; mean standardized uptake value, SULmean; mean standardized uptake value corrected for lean body mass, SULjmean; mean standardized uptake value corrected for Japanese lean body mass, SD; standard deviation

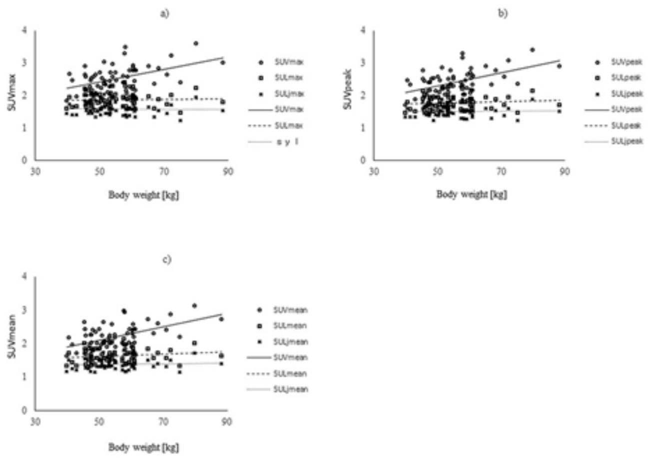

Figure 3. Correlation of SUV, SUL and SULj with body weight in patients with breast cancer (females only). a) Max value. b) Peak value. c) Mean value.

Standardized uptake value max showed a significant correlation with body weight (r=0.48, P<0.01), whereas SULmax (r=0.05, P=0.79) and SULjmax (r=-0.02, P=0.90) did not. Although a significant difference regarding the correlation coefficient (r) between SUVmax and SULjmax (P<0.01), and SUVmax and SULmax (P<0.05) was observed, that between SULmax and SULjmax was not significantly different (P=0.71). Standardized uptake value peak was also significantly correlated with body weight (r=0.52, P<0.01), whereas SULpeak (r=0.11, P=0.56) and SULjpeak (r=-0.04, P=0.84) showed no correlation. There was a significant difference for correlation coefficient (r) between SUVpeak and SULjpeak (P<0.01), and SUVpeak and SULpeak (P<0.05), whereas no such significant difference was seen between and SULpeak and SULjpeak (P=0.71). Standardized uptake value mean also showed a significant correlation with body weight (r= 0.55, P<0.01), whereas none was seen between SULmean (r= 0.15, P=0.84) and SULjmean (r=0.05, P=0.78). There was a significant difference regarding the correlation coefficient (r) between SUVmean and SULjmean (P<0.01), and SUVmean and SULmean (P<0.05), whereas that was not seen between SULmean and SULjmean (P=0.59).

The values of the slope of the regression line for SUVmax, SULmax and SULjmax were 0.0194, 0.0012, and -0.0005, respectively, for SUVpeak, SULpeak, and SULjpeak were 0.02, 0.0025, and 0.0007, respectively and for SUVmean, SULmean and SULjmean were 0.0198, 0.0033, and 0.0009, respectively. There was no significant difference between any of the indexes in regard to these values.

All patients

Results showing correlations of the maximum, peak, and average values of SUV, SUL and SULj with body weight in 172 PET/CT examinations of 86 patients (30 males with esophageal cancer, 30 females with breast cancer) are shown in Table 4 and Figure 4. Body weight ranged from 38.2 to 88.4kg, with a mean value of 56.7±9.2kg.

Standardized uptake value max showed a significant correlation with body weight (r=0.37, P<0.01), whereas SULmax (r=0.12, P=0.24) and SULjmax (r=0.04, P=0.72) did not. Although a significant difference regarding the correlation coefficient (r) was seen between SUVmax and SULjmax (P<0.01), and SUVmax and SULmax (P<0.05), no such significant difference was seen between SULmax and SULjmax (P=0.46). Standardized uptake value peak was also significantly correlated with body weight (r=0.40, P<0.01), whereas SULpeak (r=0.17, P=0.12) and SULjpeak (r=-0.04, P=0.72) were not. There was a significant difference for the correlation coefficient (r) between SUVpeak and SULjpeak (P<0.01), and SUVpeak and SULpeak (P<0.05), whereas no such significant difference was seen between and SULpeak and SULjpeak (P=0.23). Standardized uptake value mean also showed a significant correlation with body weight (r=0.41, P<0.01), whereas SULmean (r=0.19, P=0.08) and SULjmean (r=0.09, P= 0.43) did not. There was a significant difference regarding the correlation coefficient (r) between SUVmean and SULjmean (P<0.01), and SUVmean and SULmean (P<0.05), whereas that was not seen between SULmean and SULjmean (P= 0. 35).

***Table 4.** Correlation of SUV, SUL, and SULj with body weight in all patients with esophageal or breast cancer (males and females, n=86).*

	SUV max	SUL max	SUL jmax
Correlation coefficient (r)	0.37	0.12	0.04
Significance of the correlation	<0.01	0.24	0.72
	SUV peak	**SUL peak**	**SUL jpeak**
Correlation coefficient (r)	0.4	0.17	0.04
Significance of the correlation	<0.01	0.12	0.72
	SUV mean	**SUL mean**	**SUL jmean**
Correlation coefficient (r)	0.41	0.19	0.09
Significance of the correlation	<0.01	0.08	0.43

SUVmax; maximum standardized uptake value, SULmax; maximum standardized uptake value corrected for lean body mass, SULjmax; maximum standardized uptake value corrected for Japanese lean body mass, SUVpeak; peak standardized uptake value, SULpeak; peak standardized uptake value corrected for lean body mass, SULjpeak; peak standardized uptake value corrected for Japanese lean body mass, SUVmean; mean standardized uptake value, SULmean; mean standardized uptake value corrected for lean body mass, SULjmean; mean standardized uptake value corrected for Japanese lean body mass, SD; standard deviation

The values of the slope of the regression line for SUVmax, SULmax and SULjmax were 0.0139, 0.004, and 0.0012, respectively, for SUVpeak, SULpeak and SULjpeak were 0.0144, 0.0051, and 0.0023, respectively, and for SUVmean, SULmean and SULjmean were 0.014, 0.0056, and 0.0024, respectively, and for SUVmean, SULmean and SULjmean were 0.014, 0.0056, and 0.0024, respectively. There was no significant difference between any of the indexes in regard to these values.

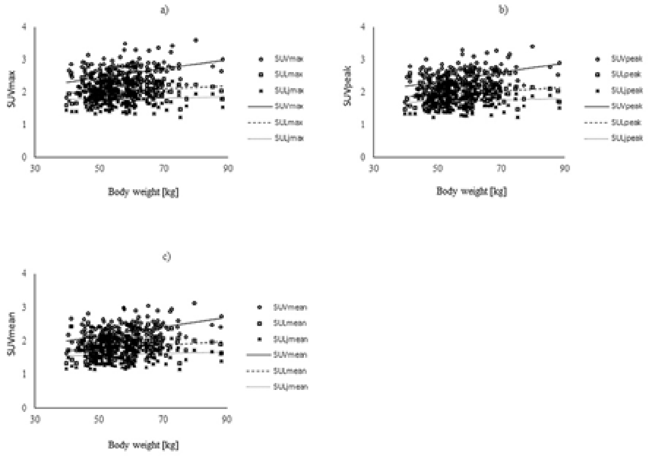

Figure 4. Correlation of SUV, SUL, and SULj with body weight in all patients. a) Max value. b) Peak value. c) Mean value.

Discussion

The present study was conducted to evaluate the correlation of quantitative indexes, such as SUV, SUL, and SULj, with body weight for assessment of response to cancer treatment in Japanese patients on ^{18}F-FDG PET findings. Our results revealed that maximum, peak, and average SUV are dependent on body weight, whereas those values for SUL and SULj do not vary with body weight fluctuations, regardless of type of cancer or gender. Moreover, the maximum, peak, and average SULj values each showed a lower level of correlation with body weight as compared to those of SUL, regardless of type of cancer or gender.

Standardized uptake value was previously reported to be affected by the physique of the subject, with similar results obtained in two studies [13, 14], whereas SUL and SULj were not correlated with body weight, cancer type, or gender in the present series. Therefore, use of these indices makes it possible to evaluate treatment response in patients with various types of cancers using ^{18}F-FDG PET/CT findings without concern for weight fluctuation, type of cancer, or gender.

In conclusion, based on the correlation with body weight and slope value of the regression line, we consider that either SUL or SULj (SUL corrected for Japanese lean body mass) can be used for the assessment of treatment response in Japanese cancer patients using ^{18}F-FDG PET/CT findings.

The authors declare that they have no conflicts of interest.

Acknowledgement
We are grateful to all patients who contributed to this study.

Bibliography

1. Imperiale A, Cimarelli S, Brigand C et al. Does the association of ^{18}F-FDG uptake intensity and lesion topography reveal histological phenotype and tumor differentiation in esophageal cancer? *Hell J Nucl Med* 2011; 14(3): 239-42.
2. Zhang X, Wu F, Han P. The role of ^{18}F-FDG PET/CT in the diagnosis of breast cancer and lymph nodes metastases and micrometastases may be limited. *Hell J Nucl Med* 2014; 17(3): 177-83.
3. Mittal BR, Manohar K, Kashyap R et al. The role of ^{18}F-FDG PET/CT in initial staging of patients with locally advanced breast carcinoma with an emphasis on M staging. *Hell J Nucl Med* 2011; 14(2): 135-9.
4. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. *J Nucl Med* 2009; 50(1 suppl): 122-50.
5. Ito H, Ohshima A, Ohto N et al. Relation between body composition and age in healthy Japanese subjects. *Eur J Clin Nutr* 2001; 55: 462-70.
6. Odawara S, Kitajima K, Katuura T et al. Tumor response to neoadjuvant chemotherapy in patients with esophageal cancer assessed with CT and FDG-PET/CT -RECIST 1.1 vs. PERCIST 1.0. *Eur J Radiol* 2018; 101: 65-71.
7. Kitajima K, Nakatani K, Yamaguchi K et al. Response to neoadjuvant chemotherapy for breast cancer judged by PERCIST -multicenter study in Japan. *Eur J Nucl Med Mol Imaging* 2018; 45: 1661-71.
8. Katuura T, Kitajima K, Fujiwara M et al. Assessment of tumor response to chemoradiotherapy and predicting prognosis in patients with head and neck squamous cell carcinoma by PERCIST. *Ann Nucl Med* 2018; 32: 453-62.
9. Kitajima K, Miyoshi Y, Yamano T et al. Assessment of tumor response to neoadjuvant chemotherapy in patients with breast cancer using MRI and FDG-PET/CT -RECIST 1.1 vs. PERCIST 1.0. *Nagoya J Med Sci* 2018; 80: 183-97.
10. Adams MC, Turkington TG, Wilson JM, Wong TZ. A systematic review of the factors affecting accuracy of SUV measurements. *Am J Roentgenol* 2010; 195: 310-20.
11. Keyes JW. SUV: standard uptake or silly useless value? *J Nucl Med* 1995; 36: 1836-9.
12. Westerterp M, Pruim J, Oyen W et al. Quantification of FDG PET studies using standardised uptake values in multi-centre trials: effects of image reconstruction, resolution and ROI definition parameters. *Eur J Nucl Med Mol Imaging* 2007; 34: 392-404.
13. Sugawara Y, Zasadny KR, Neuhoff AW, Wahl RL. Reevaluation of the standardized uptake value for FDG: variations with body weight and methods for correction. *Radiology* 1999; 213: 521-5.
14. Zasadny KR, Wahl RL. Standardized uptake values of normal tissues at PET with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose: variations with body weight and a method for correction. *Radiology* 1993; 189: 847-50.